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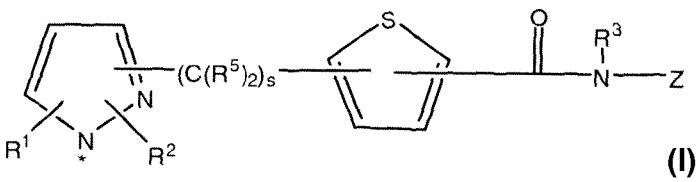

(I)

(57) Abstract: The present invention relates to compounds of the general formula (I): wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and are as defined herein, to compositions comprising the compounds, and methods of using the compounds as glucagon receptor antagonists and for the treatment or prevention of type 2 diabetes and conditions related thereto.

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THIOPHENES AS GLUCAGON RECEPTOR ANTAGONISTS, COMPOSITIONS, AND METHODS FOR THEIR USE

FIELD OF THE INVENTION

The present invention relates to certain novel compounds as glucagon receptor antagonists, compositions comprising these compounds, and methods for their use in treating, preventing, or delaying the onset of type 2 diabetes and related conditions.

BACKGROUND OF THE INVENTION

Diabetes refers to a disease state or process derived from multiple causative factors and is characterized by elevated levels of plasma glucose (hyperglycemia) in the fasting state or after administration of glucose during a glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with a wide range of pathologies. Frank diabetes mellitus (e.g., fasting blood glucose levels above about 126 mg/dL) is associated with increased and premature cardiovascular disease and premature mortality, and is related directly and indirectly to various metabolic conditions, including alterations of lipid, lipoprotein, apolipoprotein metabolism and other metabolic and hemodynamic diseases. As such, the diabetic patient is at increased risk of macrovascular and microvascular complications. Such complications can lead to diseases and conditions such as coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Accordingly, therapeutic control and correction of glucose homeostasis is regarded as important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), the diabetic patient's pancreas is incapable of producing adequate amounts of insulin, the hormone which regulates glucose uptake and utilization by cells. In type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often produce plasma insulin levels comparable to those of nondiabetic subjects; however, the cells of

patients suffering from type 2 diabetes develop a resistance to the effect of insulin, even in normal or elevated plasma levels, on glucose and lipid metabolism, especially in the main insulin-sensitive tissues (muscle, liver and adipose tissue).

Insulin resistance is not associated with a diminished number of cellular insulin receptors but rather with a post-insulin receptor binding defect that is not well understood. This cellular resistance to insulin results in insufficient insulin activation of cellular glucose uptake, oxidation, and storage in muscle, and inadequate insulin repression of lipolysis in adipose tissue, and of glucose production and secretion in the liver. A net effect of decreased sensitivity to insulin is high levels of insulin circulating in the blood without appropriate reduction in plasma glucose (hyperglycemia). Hyperinsulinemia is a risk factor for developing hypertension and may also contribute to vascular disease.

The available treatments for type 2 diabetes, some of which have not changed substantially in many years, are used alone and in combination. Many of these treatments have recognized limitations, however. For example, while physical exercise and reductions in dietary intake of fat, high glycemic carbohydrates, and calories can dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic beta-cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate insulin-resistance in tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance due to the even higher plasma insulin levels can occur. The biguanides are a separate class of agents that can increase insulin sensitivity and bring about some degree of correction of hyperglycemia. These agents, however, can induce lactic acidosis, nausea and diarrhea.

The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are another class of compounds that have proven useful for the treatment of type 2 diabetes.

These agents increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes, resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensititization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type II diabetes are agonists of the alpha, gamma or delta subtype, or a combination thereof, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have been noted in some patients treated with glitazone drugs, such as troglitazone.

Compounds that are inhibitors of the dipeptidyl peptidase-IV (DPP-IV) enzyme are also under investigation or available as drugs for the treatment of diabetes, and particularly type 2 diabetes. Examples include alogliptin (Takeda), saxagliptin (Brystol-Myers Squibb), sitagliptin (Januvia™, Merck), vildagliptin (Galvus™, Novartis), denagliptin (GlaxoSmithKline), ABT-279 and ABT-341 (Abbott), ALS-2-0426 (Alantos), ARI-2243 (Arisaph), BI-A and BI-B (Boehringer Ingelheim), SYR-322 (Takeda), compounds disclosed in US Patent No. 6,699,871, MP-513 (Mitsubishi), DP-893 (Pfizer), RO-0730699 (Roche) and combinations thereof.

Additional methods of treating hyperglycemia and diabetes are currently under investigation. New biochemical approaches include treatment with alpha-glucosidase inhibitors (e.g. acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

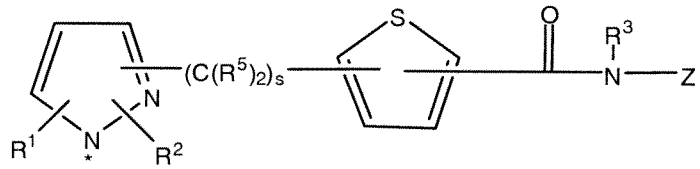
Other approaches to treating hyperglycemia, diabetes, and indications attendant thereto have focused on the glucagon hormone receptor. Glucagon and insulin are the two primary hormones regulating plasma glucose levels. Insulin, released in response to a meal, increases the uptake of glucose into insulin-sensitive tissues such as skeletal muscle and fat. Glucagon, which is secreted by alpha cells in pancreatic islets in response to decreased postprandial glucose levels or during fasting, signals the production and release of glucose from the liver. Glucagon binds to specific receptors in liver cells that trigger glycogenolysis and an increase in gluconeogenesis through cAMP-mediated

events. These responses generate increases in plasma glucose levels (e.g., hepatic glucose production), which help to regulate glucose homeostasis.

Type 2 diabetic patients typically have fasting hyperglycemia that is associated with elevated rates of hepatic glucose production. This is due to increased gluconeogenesis coupled with hepatic insulin resistance. Such patients typically have a relative deficiency in their fasting and postprandial insulin-to-glucagon ratio that contributes to their hyperglycemic state. Several studies have demonstrated that hepatic glucose production correlates with fasting plasma glucose levels, suggesting that chronic hepatic glucagon receptor antagonism should improve this condition. In addition, defects in rapid postprandial insulin secretion, as well as ineffective suppression of glucagon secretion, lead to increased glucagon levels that elevate hepatic glucose production and contribute to hyperglycemia. Suppression of elevated postprandial glucagon levels in type 2 diabetics with somatostatin has been shown to lower blood glucose concentrations. This indicates that acute postprandial glucagon receptor antagonism would also be beneficial. Based on these and other data, glucagon receptor antagonism holds promise as a potential treatment of type 2 diabetes by reducing hyperglycemia. There is thus a need in the art for small-molecule glucagon receptor antagonists with good safety profiles and efficacy that are useful for the treatment of hyperglycemia, diabetes, and related metabolic diseases and indications. The present invention addresses that need.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a compound, or a pharmaceutically acceptable salt, solvate, ester, prodrug, tautomer, or isomer of said compound, said compound having the general structure shown in Formula (A):

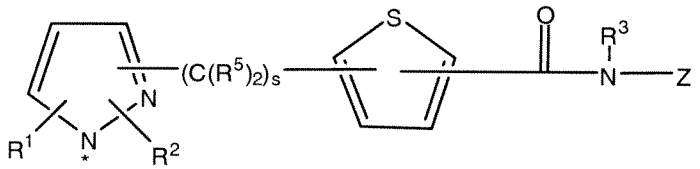


(A)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and are as defined below. These and other embodiments are described in more detail below.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention provides a compound, or a pharmaceutically acceptable salt, solvate, ester, prodrug, tautomer, or isomer of said compound, said compound having the general structure shown in Formula (A):



(A)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

the * shown in the N* represents a valence optionally filled by R^1, R^2, or H;

s is an integer from 1 to 5;

R^1 is selected from the group consisting of:

(a) $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-C(O)NR^8R^9$, and $-NR^8R^9$;

(b) alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl,

-O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, $-OC(O)NR^8R^9$, unsubstituted alkoxy, and alkoxy substituted with one or more groups independently selected from the group consisting of halo, perhaloalkoxy, OH, and $-CO_2R^6$;

(c) -O-aryl, -S-aryl, arylalkyl-, -O-heteroaryl, -S-heteroaryl, heteroarylalkyl-, cycloalkyl, aryl-fused cycloalkyl-, cycloalkylalkyl-, -O-cycloalkyl, -S-cycloalkyl, heterocycloalkyl, aryl-fused heterocycloalkyl-, heterocycloalkylalkyl-, -O-heterocycloalkyl, -S-heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, -S-cycloalkenyl, heterocycloalkenyl, -O-heterocycloalkenyl, and -S-heterocycloalkenyl,

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl portions of said -O-aryl, -S-aryl, arylalkyl-, -O-heteroaryl, -S-heteroaryl, heteroarylalkyl-, cycloalkyl, aryl-fused cycloalkyl-, cycloalkylalkyl-, -O-cycloalkyl, -S-cycloalkyl, heterocycloalkyl, aryl-fused heterocycloalkyl-, heterocycloalkylalkyl-, -O-heterocycloalkyl, -S-heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, -S-cycloalkenyl, heterocycloalkenyl, -O-heterocycloalkenyl, and -S-heterocycloalkenyl, and the alkyl portions of said arylalkyl-, said heteroarylalkyl-, said cycloalkylalkyl-, and said heterocycloalkylalkyl-, are each independently

unsubstituted or optionally independently substituted with 1 or more groups each independently selected from the group consisting of:

(i) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^8-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(ii) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(iii) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (i) and (ii) above;

and

(d) aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SF_5$, $-Si(R^7)_3$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(2) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above;

R^2 is selected from the group consisting of aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein the aryl and heteroaryl, and the aryl and heteroaryl portions of said arylalkyl- and said heteroarylalkyl-, are substituted with 1 or more groups each independently selected from the group consisting of:

(A) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SF_5$, $-Si(R^7)_3$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(B) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

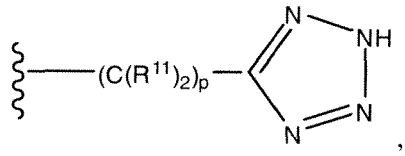
wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

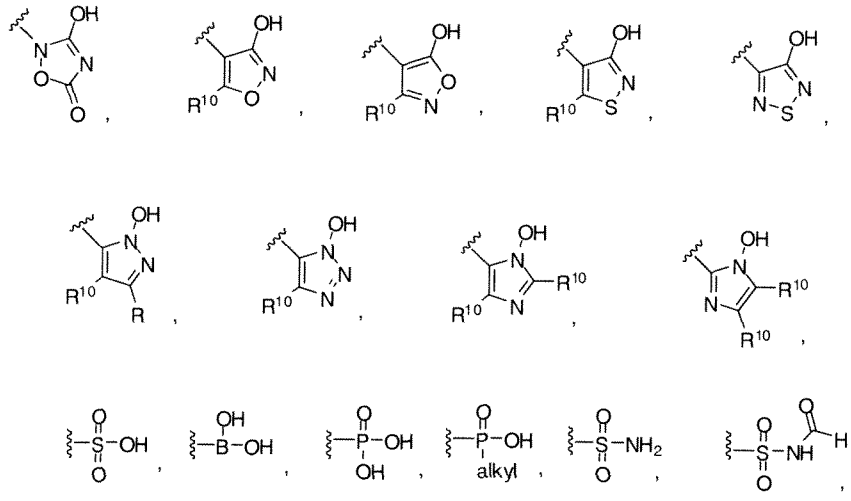
(C) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally

independently substituted with from 1 to 2 groups each independently selected from (A) and (B) above;

R^3 is selected from the group consisting of H and lower alkyl;

Z is a moiety selected from $-(C(R^{11})_2)-(C(R^{12}R^{13}))_m-C(O)OH$, $-(C(R^{11})_2)-(C(R^{14})_2)_n-C(O)OH$, from $-(C(R^{11})_2)-(C(R^{12}R^{13}))_m-C(O)Oalkyl$, $-(C(R^{11})_2)-(C(R^{14})_2)_n-C(O)Oalkyl$,  , $-(C(R^{11})_2)-(C(R^{12}R^{13}))_m-Q$, and $-(C(R^{11})_2)-(C(R^{14})_2)_n-Q$,

wherein Q is a moiety selected from the group consisting of:



;

m is an integer from 0 to 5;

n is an integer from 0 to 5;

p is an integer from 0 to 5;

each R^5 is independently selected from the group consisting of H, lower alkyl, hydroxy-substituted lower alkyl;

each R^6 is independently selected from the group consisting of H and alkyl;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, arylalkyl-;

each R^8 is independently selected from the group consisting of H and alkyl;

each R^9 is independently selected from the group consisting of H and alkyl,

or alternatively R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered saturated heterocyclic ring, or a 5-, 6-, or 7-membered unsaturated heterocyclic ring, which ring contains (including said nitrogen) from 1 to 2 ring heteroatoms each independently selected from the group consisting of N, N-oxide, O, S, S(O), or $S(O)_2$,

or alternatively R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-membered heteroaromatic ring containing (including the nitrogen to which R^8 and R^9 are attached) from 1 to 3 ring nitrogens;

each R^{10} is independently selected from the group consisting of H and alkyl;

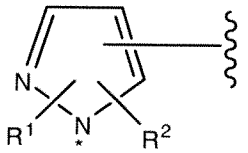
each R^{11} is independently selected from the group consisting of H and lower alkyl;

each R^{12} is independently selected from the group consisting of H, lower alkyl, -OH, hydroxy-substituted lower alkyl;

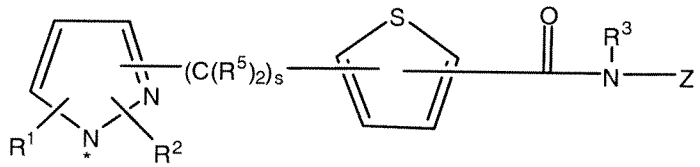
each R^{13} is independently selected from the group consisting of H, unsubstituted lower alkyl, lower alkyl substituted with one or more groups each independently selected from the group consisting of hydroxyl and alkoxy, or R^{12} and R^{13} are taken together to form an oxo; and

each R^{14} is independently selected from the group consisting of H and fluoro.

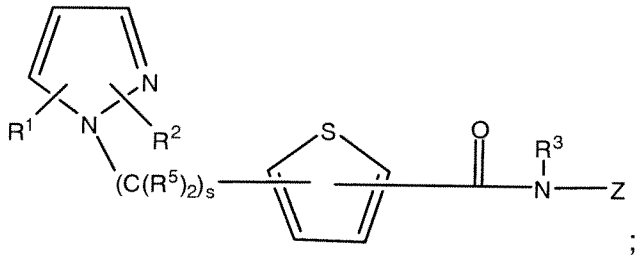
It shall be understood that the *shown in the pyrazole moiety,



, in the general formulas of the compounds of the invention, e.g., in Formula (A), indicates a valence which is optionally filled by R^1, R^2, the $-(C(R^5)_2)_s-$ group shown, or H. Thus, the formula



represents any of the following formulas:



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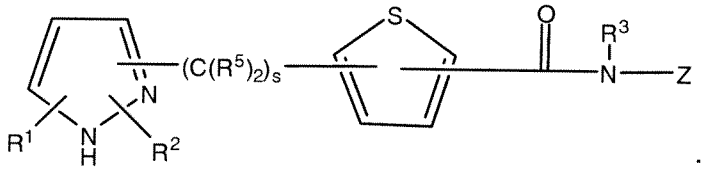

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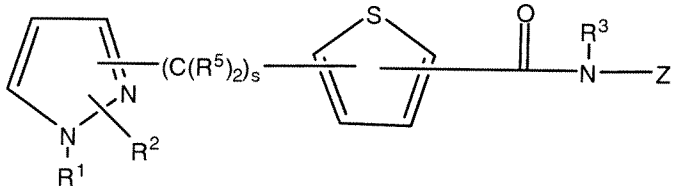
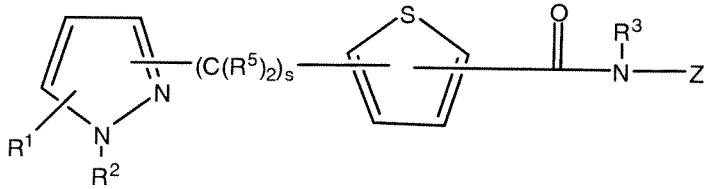


; and/or



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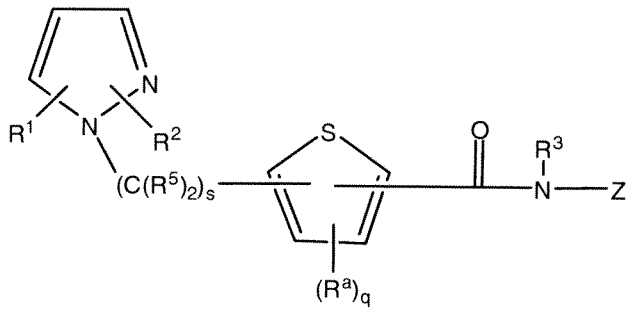
In one embodiment, the present invention provides a compound, or a pharmaceutically acceptable salt, solvate, ester, prodrug, tautomer, or isomer of said compound, said compound having the general structure shown in Formula (I):



(I)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

s is an integer from 0 to 2;

each R^a (when present) is independently selected from the group consisting of halo, alkyl, and haloalkyl;

q is 0 to 2;

R^1 is selected from the group consisting of:

(a) $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-C(O)NR^8R^9$, and $-NR^8R^9$;

(b) alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$,

$-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, $-OC(O)NR^8R^9$, unsubstituted alkoxy, and alkoxy substituted with one or more groups independently selected from the group consisting of halo, perhaloalkoxy, OH, and $-CO_2R^6$;

(c) -O-aryl, -S-aryl, arylalkyl-, -O-heteroaryl, -S-heteroaryl, heteroarylalkyl-, cycloalkyl, aryl-fused cycloalkyl-, cycloalkylalkyl-, -O-cycloalkyl, -S-cycloalkyl, heterocycloalkyl, aryl-fused heterocycloalkyl-, heterocycloalkylalkyl-, -O-heterocycloalkyl, -S-heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, -S-cycloalkenyl, heterocycloalkenyl, -O-heterocycloalkenyl, and -S-heterocycloalkenyl,

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl portions of said -O-aryl, -S-aryl, arylalkyl-, -O-heteroaryl, -S-heteroaryl, heteroarylalkyl-, cycloalkyl, aryl-fused cycloalkyl-, cycloalkylalkyl-, -O-cycloalkyl, -S-cycloalkyl, heterocycloalkyl, aryl-fused heterocycloalkyl-, heterocycloalkylalkyl-, -O-heterocycloalkyl, -S-heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, -S-cycloalkenyl, heterocycloalkenyl, -O-heterocycloalkenyl, and -S-heterocycloalkenyl, and the alkyl portions of said arylalkyl-, said heteroarylalkyl-, said cycloalkylalkyl-, and said heterocycloalkylalkyl-, are each independently unsubstituted or optionally independently substituted with 1 or more groups each independently selected from the group consisting of:

(i) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^8-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(ii) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl,

-O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(iii) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from the group consisting of (i) and (ii) above;

and

(d) aryl and heteroaryl,

wherein each of said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SF_5$, $-Si(R^7)_3$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(2) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above;

R^2 is selected from the group consisting of aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein the aryl and heteroaryl, and the aryl and heteroaryl portions of said arylalkyl- and heteroarylalkyl-, are substituted with 1 or more groups each independently selected from the group consisting of:

(A) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SF_5$, $-Si(R^7)_3$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(B) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl,

-heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

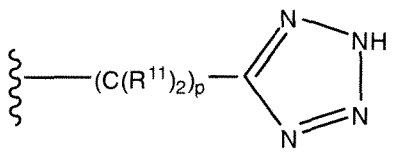
wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(C) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (A) and (B) above;

R^3 is selected from the group consisting of H and lower alkyl;

Z is a moiety selected from the group consisting of $-(C(R^{11})_2)-(C(R^{12}R^{13}))_m-C(O)OH$, $-(C(R^{11})_2)-(C(R^{14})_2)_n-C(O)OH$, and



;

m is an integer from 0 to 5;

n is an integer from 0 to 5;

p is an integer from 0 to 5;

each R^5 is independently selected from the group consisting of H, lower alkyl, hydroxy-substituted lower alkyl;

each R^6 is independently selected from the group consisting of H and alkyl;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, arylalkyl-;

each R^8 is independently selected from the group consisting of H and alkyl;

each R^9 is independently selected from the group consisting of H and alkyl,

or alternatively R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered saturated heterocyclic ring, or a 5-, 6-, or 7-membered unsaturated heterocyclic ring, which ring contains (including said nitrogen) from 1 to 2 ring heteroatoms each independently selected from the group consisting of N, N-oxide, O, S, S(O), or $S(O)_2$,

or alternatively R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-membered heteroaromatic ring containing (including the nitrogen to which R^8 and R^9 are attached) from 1 to 3 ring nitrogens;

each R^{10} is independently selected from the group consisting of H and alkyl;

each R^{11} is independently selected from the group consisting of H and lower alkyl;

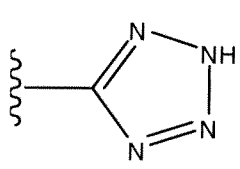
each R^{12} is independently selected from the group consisting of H, lower alkyl, -OH, hydroxy-substituted lower alkyl;

each R^{13} is independently selected from the group consisting of H, unsubstituted lower alkyl, lower alkyl substituted with one or more groups each independently selected from the group consisting of hydroxyl and alkoxy, or R^{12} and R^{13} are taken together to form an oxo; and

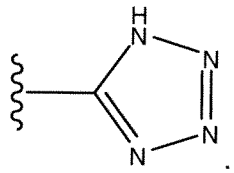
each R^{14} is independently selected from the group consisting of H and fluoro.

As indicated above, tautomers of the compounds of the various formulas of the invention described herein are embraced by the present invention. For

example, it shall be understood that tetrazoles (such as those described in variable "Z") written as:



also embrace



.

In one embodiment, in Formula (I), q is 0.

In one embodiment, in Formula (I), q is 1.

In one embodiment, in Formula (I), q is 2.

In one embodiment, in Formula (I), $-(C(R^5)_2)_s-$ is selected from the group consisting of $-(C(CH_3)_2)_s-$, $-(CH(CH_3))_s-$, and $-(CH_2)_s-$, wherein s is 1-3.

In one embodiment, in Formula (I), $-(C(R^5)_2)_s-$ is selected from the group consisting of $-(C(CH_3)_2)_s-$, $-(CH(CH_3))_s-$, and $-(CH_3)_s-$, wherein s is 1-2.

In one embodiment, in Formula (I), $-(C(R^5)_2)_s-$ is selected from the group consisting of $-(C(CH_3)_2)_s-$, $-(CH(CH_3))_s-$, and $-(CH_2)_s-$, wherein s is 1.

In one embodiment, in Formula (I), $-(C(R^5)_2)_s-$ is selected from the group consisting of $-(CH(CH_3))_s-$ and $-(CH_2)_s-$, wherein s is 1.

In one embodiment, in Formula (I), $-(C(R^5)_2)_s-$ is $-(CH(CH_3))-$.

In one embodiment, in Formula (I), R^1 is selected from the group consisting of:

(a) $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-C(O)NR^8R^9$, and $-NR^8R^9$,

(b) $-(C_{4-6})$alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -alkynyl, -C(O)alkynyl, and -C(O)-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said $-(C_{4-6})$alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -alkynyl, -C(O)alkynyl, and -C(O)-heteroalkynyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$,

-C(O)NR^8R^9, -OC(O)NR^8R^9, unsubstituted alkoxy, and alkoxy substituted with one or more groups independently selected from the group consisting of halo, perhaloalkoxy, OH, and -CO_2R^6,

(c) arylalkyl-, cycloalkylalkyl-, heteroarylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, cycloalkenyl, and heterocycloalkenyl,

wherein each of said arylalkyl-, said cycloalkylalkyl-, said heteroarylalkyl-, said heterocycloalkyl, said heterocycloalkylalkyl-, said cycloalkenyl, and said heterocycloalkenyl, and the alkyl portions of said arylalkyl-, said cycloalkylalkyl-, said heteroarylalkyl-, and said heterocycloalkylalkyl-, are each unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

(i) halo, OH, -CO_2R^6, -C(O)R^6, -SR^7, -S(O)R^7, -SO_2R^7, CN, -C(O)NR^8R^9, -NR^8R^9, haloalkoxy, -NR^{10}-C(O)-NR^8R^9, -NR^{10}-CO_2R^6, -NR^{10}-C(O)R^6, -NR^{10}-SO_2R^6, -SO_2-NR^8R^9, -C(O)NR^8R^9, and -OC(O)NR^8R^9,

(ii) -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, -CO_2R^6, -C(O)R^6, -SR^7, -S(O)R^7, -SO_2R^7, CN, NO_2, -C(O)NR^8R^9, -NR^8R^9, haloalkoxy, -NR^{10}-C(O)-NR^8R^9, -NR^{10}-CO_2R^6, -NR^{10}-C(O)R^6, -NR^{10}-SO_2R^6, -SO_2-NR^8R^9, -C(O)NR^8R^9, and -OC(O)NR^8R^9, and

(iii) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, cycloalkenyl,

-O- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (i) and (ii) above, and

(d) aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, $-C(O)R^6$, CN, $-C(O)NR^8R^9$, haloalkoxy, and $-C(O)NR^8R^9$,

(2) -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)-heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)-cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above.

In one embodiment, in Formula (I), R^1 is selected from the group consisting of:

(a) $-SR^7$, $-C(O)NR^8R^9$, and $-NR^8R^9$,

(b) -alkenyl, and –alkynyl,

wherein each of said alkenyl and said alkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, $-OC(O)NR^8R^9$, unsubstituted alkoxy, and alkoxy substituted with one or more groups independently selected from the group consisting of halo, perhaloalkoxy, OH, and $-CO_2R^6$,

(c) cycloalkenyl and heterocycloalkenyl,

wherein each of said cycloalkenyl and said heterocycloalkenyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

(i) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(ii) -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(iii) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (i) and (ii) above, and

(d) aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, CN, $-C(O)NR^8R^9$, haloalkoxy, and $-C(O)NR^8R^9$,

(2) -alkyl, -O-alkyl, and -alkenyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -O-alkyl, and -alkenyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, heterocycloalkenyl, and -O-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above.

In one embodiment, in Formula (I), R^1 is selected from the group consisting of:

aryl and heteroaryl,

wherein each of said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

halo, alkyl, haloalkyl, heteroalkyl, alkenyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkenyl, -O-cycloalkyl, and -O-cycloalkenyl.

In one embodiment, in Formula (I), R^1 is selected from the group consisting of:

phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with at least one group each independently selected from the group consisting of:

halo, alkyl, cycloalkyl, haloalkyl, alkoxy, and haloalkoxy.

In one embodiment, in Formula (I), R^2 is selected from the group consisting of:

aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, $-C(O)R^6$, CN, $-C(O)NR^8R^9$, haloalkoxy, and $-C(O)NR^8R^9$,

(2) -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl,

wherein the alkyl, alkenyl and alkynyl portions of said -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl, are unsubstituted or optionally independently substituted with one or more groups

each independently selected from the group consisting of:
halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)-heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)-cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above.

In one embodiment, in Formula (I), R^2 is selected from the group consisting of the group consisting of:

aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein said aryl and said heteroaryl, and the aryl and heteroaryl portions of said arylalkyl- and said heteroarylalkyl-, are substituted with at least one group each independently selected from the group consisting of:

(1) halo, CN, $-C(O)NR^8R^9$, haloalkoxy, and $-C(O)NR^8R^9$,

(2) -alkyl, -O-alkyl, and -alkenyl,

wherein the alkyl, alkenyl and alkynyl portions of said -alkyl, -O-alkyl, and -alkenyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:
halo, OH, $-CO_2R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, heterocycloalkenyl, and -O-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above.

In one embodiment, in Formula (I), R^2 is selected from the group consisting of:

aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein said aryl and said heteroaryl, and the aryl and heteroaryl portions of said arylalkyl- and said heteroarylalkyl-, are substituted with at least one group each independently selected from the group consisting of:

halo, alkyl, haloalkyl, heteroalkyl, alkenyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkenyl, -O-cycloalkyl, and -O-cycloalkenyl.

In one embodiment, in Formula (I), R^2 is selected from the group consisting of:

aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

halo, alkyl, haloalkyl, heteroalkyl, alkenyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkenyl, -O-cycloalkyl, and -O-cycloalkenyl.

In one embodiment, in Formula (I), R^2 is selected from the group consisting of:

phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with at least one group each independently selected from the group consisting of:

halo, alkyl, cycloalkyl, haloalkyl, alkoxy, and haloalkoxy.

In one embodiment, in Formula (I), R^3 is H.

In one embodiment, in Formula (I), R^3 is selected from the group consisting of methyl, ethyl, n-propyl, and isopropyl.

In one embodiment, in Formula (I), each R^8 is independently selected from the group consisting of H and alkyl.

In one embodiment, in Formula (I), each R^9 is independently selected from the group consisting of H and alkyl.

In one embodiment, in Formula (I), R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered heteroaromatic ring, which ring contains (including said nitrogen to which R^8 and R^9 are attached) from 1 to 2 ring heteroatoms.

In one embodiment, in Formula (I), R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered saturated heterocyclic ring, which ring contains (including said nitrogen to which R^8 and R^9 are attached) from 1 to 2 ring heteroatoms.

In one embodiment, in Formula (I), R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered partially or fully unsaturated heterocyclic ring, which ring contains (including said nitrogen to which R^8 and R^9 are attached) form 1 to 2 ring heteroatoms.

In one embodiment, in Formula (I), R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, or 6-membered saturated, or partially or fully unsaturated, heterocyclic ring, which ring contains (including said nitrogen to which R^8 and R^9 are attached) form 1 to 2 ring heteroatoms.

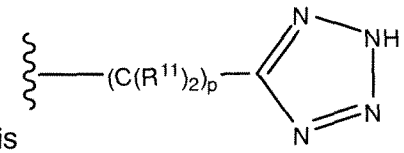
In one embodiment, in Formula (I), R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered ring moiety, non-limiting examples of such moieties include pyrrolidine, imidazolidine, piperazine, morpholine, thiomorpholine, oxazolidine, and thiazolidine.

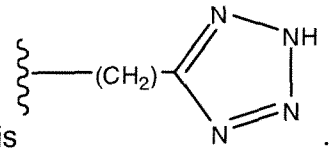
In one embodiment, in Formula (I), Z is $-(C(R^{11})_2)-(C(R^{12})(R^{13}))_m-C(O)OH$.

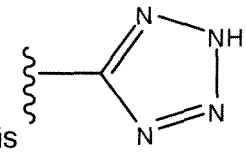
In one embodiment, in Formula (I), Z is $-(CH_2)-(CH(CH_3))-C(O)OH$.

In one embodiment, in Formula (I), Z is -(CH_2)-(CH_2)-(CH_2)-C(O)OH.
In one embodiment, in Formula (I), Z is -(CH_2)-$C(CH_3)_2$-C(O)OH.
In one embodiment, in Formula (I), Z is -(CH_2)-$C(CH_3)$(OH)-C(O)OH.
In one embodiment, in Formula (I), Z is -CH_2-CH_2-C(O)OH.
In one embodiment, in Formula (I), Z is -CH_2-CH(OH)-C(O)OH.
In one embodiment, in Formula (I), Z is -$CH(CH_3)$-CH_2-C(O)OH.
In one embodiment, in Formula (I), Z is -$C(CH_3)_2$-CH_2-C(O)OH.

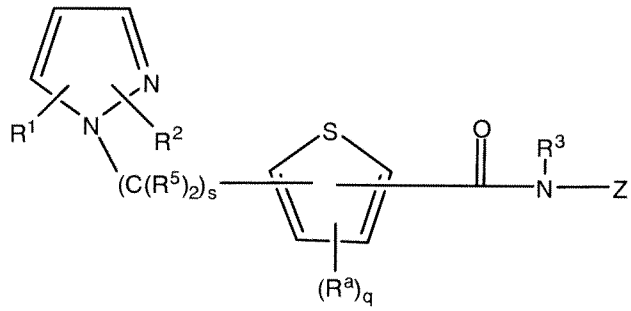
In one embodiment, in Formula (I), Z is -$(C(R^{11})_2)$-$(C(R^{14})_2)_n$-C(O)OH.
In one embodiment, in Formula (I), Z is -CH_2-CH(F)-C(O)OH.
In one embodiment, in Formula (I), Z is -CH_2-CF_2-C(O)OH.
In one embodiment, in Formula (I), Z is -$CH(CH_3)$-CF_2-C(O)OH.
In one embodiment, in Formula (I), Z is -CH_2-CH_2-CF_2-C(O)OH.

In one embodiment, in Formula (I), Z is  .

In one embodiment, in Formula (I), Z is  .

In one embodiment, in Formula (I), Z is  .

In one embodiment, the compounds of the present invention, which include a pharmaceutically acceptable salt, solvate, ester, prodrug, tautomer, or isomer of said compound, have the general structure shown in Formula (III):



(III)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

s is 0 to 2;

each R^a (when present) is independently selected from the group consisting of halo, alkyl, and haloalkyl;

q is 0 to 1;

R^1 is selected from the group consisting of:

(a) $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-C(O)NR^8R^9$, and $-NR^8R^9$,

(b) $-(C_{4-6})$alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -alkynyl, -C(O)alkynyl, and -C(O)-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said $-(C_{4-6})$alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -alkynyl, -C(O)alkynyl, and -C(O)-heteroalkynyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, $-OC(O)NR^8R^9$, unsubstituted alkoxy, and alkoxy substituted with one or more groups independently selected from halo, perhaloalkoxy, OH, and $-CO_2R^6$,

(c) arylalkyl-, cycloalkylalkyl-, heteroarylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, cycloalkenyl, and heterocycloalkenyl,

wherein said arylalkyl-, said cycloalkylalkyl-, said heteroarylalkyl-, said heterocycloalkyl, said heterocycloalkylalkyl-, said cycloalkenyl, and said heterocycloalkenyl, and the alkyl portions of said arylalkyl-, said cycloalkylalkyl-, said heteroarylalkyl-, and said heterocycloalkylalkyl-, are each unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

(i) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(ii) -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(iii) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (i) and (ii) above, and

(d) aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, -C(O)R^6, CN, -C(O)NR^8R^9, haloalkoxy, and -C(O)NR^8R^9,

(2) -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, -CO_2R^6, -C(O)R^6, -SR^7, -S(O)R^7, -SO_2R^7, CN, -C(O)NR^8R^9, -NR^8R^9, haloalkoxy, –NR^{10}-C(O)-NR^8R^9, -NR^{10}-CO_2R^6, -NR^{10}-C(O)R^6, -NR^{10}-SO_2R^6, -SO_2-NR^8R^9, -C(O)NR^8R^9, and -OC(O)NR^8R^9, and

(3) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above;

R^2 is selected from the group consisting of:

aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein each of said aryl, said arylalkyl-, said heteroaryl, and said heteroarylalkyl- is substituted with at least one group each independently selected from the group consisting of:

(1) halo, -C(O)R^6, CN, -C(O)NR^8R^9, haloalkoxy, and -C(O)NR^8R^9,

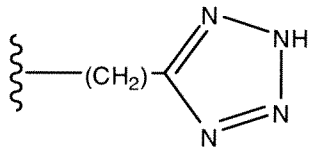
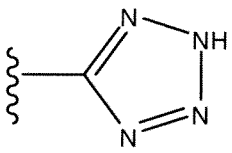
(2) -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -alkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -C(O)alkynyl, and -C(O)-heteroalkynyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, -CO_2R^6, -C(O)R^6, -SR^7, -S(O)R^7, -SO_2R^7, CN, -C(O)NR^8R^9, -NR^8R^9, haloalkoxy, –NR^{10}-C(O)-NR^8R^9, -NR^{10}-CO_2R^6, -NR^{10}-C(O)R^6, -NR^{10}-SO_2R^6, -SO_2-NR^8R^9, -C(O)NR^8R^9, and -OC(O)NR^8R^9, and

(3) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)-heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)-cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above;

Z is selected from the group consisting of -(CH_2)-(CH(CH_3))-C(O)OH, -(CH_2)-(CH_2)-(CH_2)-C(O)OH, -(CH_2)-C(CH_3)$_2$-C(O)OH, -(CH_2)-C(CH_3)(OH)-C(O)OH, -CH_2-CH_2-C(O)OH, -CH_2-CH(OH)-C(O)OH, -

$CH(CH_3)$-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -$CH(CH_3)$-CF_2-C(O)OH, -CH_2-CH_2-CF_2-C(O)OH,  , and  ;

and R^3, each R^5, each R^6, each R^7, each R^8, each R^9, each R^{10} is independently as defined in Formula (I).

In one embodiment, in Formula (III), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1-3.

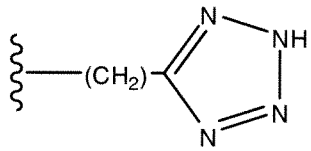
In one embodiment, in Formula (III), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1-2.

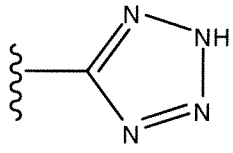
In one embodiment, in Formula (III), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1.

In one embodiment, in Formula (III), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(CH(CH_3))_s$- and –$(CH_3)_s$-, wherein s is 1.

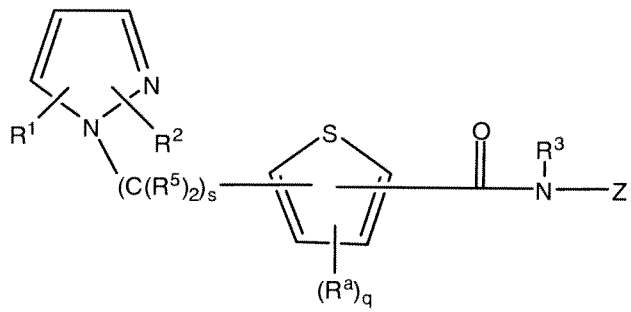
In one embodiment, in Formula (III), -$(C(R^5)_2)_s$- is -$(CH(CH_3))$-.

In one embodiment, in Formula (III), Z is selected from the group consisting of -(CH_2)-$(CH(CH_3))$-C(O)OH, -(CH_2)-(CH_2)-(CH_2)-C(O)OH, -(CH_2)-$C(CH_3)_2$-C(O)OH, -(CH_2)-$C(CH_3)$(OH)-C(O)OH, -CH_2-CH_2-C(O)OH, -CH_2-CH(OH)-C(O)OH, -$CH(CH_3)$-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -$CH(CH_3)$-CF_2-C(O)OH, and -CH_2-CH_2-CF_2-C(O)OH.

In one embodiment, in Formula (III), Z is  .

In one embodiment, in Formula (III), Z is  .

In one embodiment, the present invention provides a compound, or a pharmaceutically acceptable salt, solvate, ester, prodrug, tautomer, or isomer of said compound, said compound having the general structure shown in Formula (IV):



(IV)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

each R^a (when present) is independently selected from the group consisting of halo, alkyl, and haloalkyl;

q is 0 to 1;

R^1 is selected from the group consisting of:

(a) $-SR^7$, $-C(O)NR^8R^9$, and $-NR^8R^9$,

(b) -alkenyl, and –alkynyl,

wherein each of said alkenyl and said alkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $–NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, $-OC(O)NR^8R^9$, unsubstituted alkoxy, and alkoxy substituted with one or more groups independently selected from the group consisting of halo, perhaloalkoxy, OH, and $-CO_2R^6$,

(c) cycloalkenyl and heterocycloalkenyl,

wherein each of said cycloalkenyl and said heterocycloalkenyl are unsubstituted or optionally independently substituted with one or

more groups each independently selected from the group consisting of:

(i) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(ii) -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(iii) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)- heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (i) and (ii) above, and

(d) aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, CN, $-C(O)NR^8R^9$, haloalkoxy, and $-C(O)NR^8R^9$,

(2) -alkyl, -O-alkyl, and -alkenyl,

wherein the alkyl, alkenyl and alkynyl portions of said -alkyl, -O-alkyl, and -alkenyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, heterocycloalkenyl, and -O-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above;

R^2 is selected from the group consisting of:

aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, CN, $-C(O)NR^8R^9$, haloalkoxy, and $-C(O)NR^8R^9$,

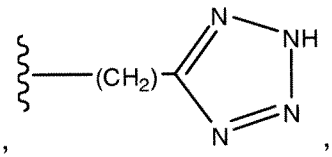
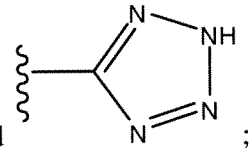
(2) -alkyl, -O-alkyl, and -alkenyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -O-alkyl, and -alkenyl, are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, heteroaryl, -O-heteroaryl, cycloalkyl, -O-cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl,

cycloalkenyl, -O-cycloalkenyl, heterocycloalkenyl, and -O-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above;

Z is selected from the group consisting of -(CH_2)-$(CH(CH_3))$-C(O)OH, -(CH_2)-(CH_2)-(CH_2)-C(O)OH, -(CH_2)-$C(CH_3)_2$-C(O)OH, -(CH_2)-$C(CH_3)$(OH)-C(O)OH, -CH_2-CH_2-C(O)OH, -CH_2-CH(OH)-C(O)OH, -$CH(CH_3)$-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -$CH(CH_3)$-CF_2-C(O)OH, -CH_2-CH_2-CF_2-C(O)OH,  , and  ;

and R^3, each R^5, each R^6, each R^7, each R^8, each R^9, each R^{10} is independently as defined in Formula (I).

In one embodiment, in Formula (IV), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1-3.

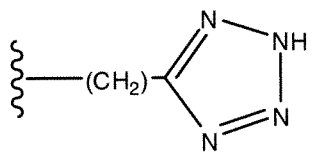
In one embodiment, in Formula (IV), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1-2.

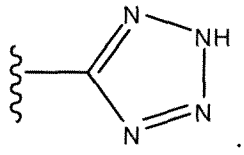
In one embodiment, in Formula (IV), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1.

In one embodiment, in Formula (IV), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(CH(CH_3))_s$- and –$(CH_2)_s$-, wherein s is 1.

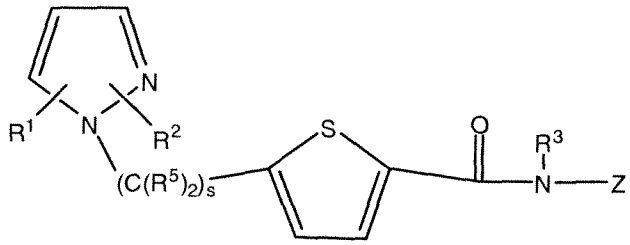
In one embodiment, in Formula (IV), -$(C(R^5)_2)_s$- is -$(CH(CH_3))$-.

In one embodiment, in Formula (IV), Z is selected from the group consisting of -(CH_2)-$(CH(CH_3))$-C(O)OH, -(CH_2)-(CH_2)-(CH_2)-C(O)OH, -(CH_2)-$C(CH_3)_2$-C(O)OH, -(CH_2)-$C(CH_3)$(OH)-C(O)OH, -CH_2-CH_2-C(O)OH, -CH_2-CH(OH)-C(O)OH, -$CH(CH_3)$-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -$CH(CH_3)$-CF_2-C(O)OH, and -CH_2-CH_2-CF_2-C(O)OH.

In one embodiment, in Formula (IV), Z is  .

In one embodiment, in Formula (IV), Z is  .

In one embodiment, the present invention provides a compound, or a pharmaceutically acceptable salt, solvate, ester, prodrug, tautomer, or isomer of said compound, said compound having the general structure shown in Formula (V):



(V)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

R^1 is selected from the group consisting of:

aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from:

halo, alkyl, haloalkyl, heteroalkyl, alkenyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkenyl, -O-cycloalkyl, and -O-cycloalkenyl;

R^2 is selected from the group consisting of:

aryl and heteroaryl,

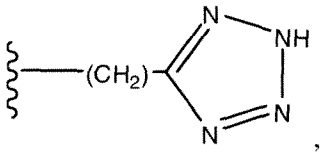
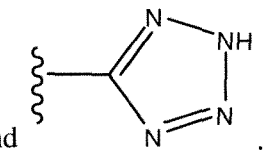
wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from:

halo, alkyl, haloalkyl, heteroalkyl, alkenyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkenyl, -O-cycloalkyl, and -O-cycloalkenyl;

R^3 is selected from the group consisting of H and lower alkyl;

R^5 is selected from the group consisting of H and lower alkyl;

S is 1 or 2;

Z is selected from the group consisting of -(CH_2)-$(CH(CH_3))$-C(O)OH, -(CH_2)-(CH_2)-(CH_2)-C(O)OH, -(CH_2)-$C(CH_3)_2$-C(O)OH, -(CH_2)-$C(CH_3)$(OH)-C(O)OH, -CH_2-CH_2-C(O)OH, -CH_2-CH(OH)-C(O)OH, -$CH(CH_3)$-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -$CH(CH_3)$-CF_2-C(O)OH, -CH_2-CH_2-CF_2-C(O)OH,  , and  .

In one embodiment, in Formula (V), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1-3.

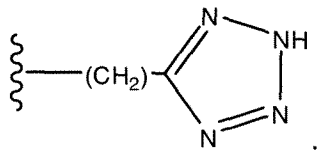
In one embodiment, in Formula (V), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1-2.

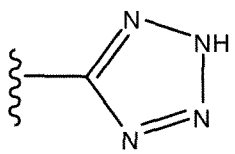
In one embodiment, in Formula (V), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1.

In one embodiment, in Formula (V), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(CH(CH_3))_s$- and –$(CH_2)_s$-, wherein s is 1.

In one embodiment, in Formula (V), -$(C(R^5)_2)_s$- is -$(CH(CH_3))$-.

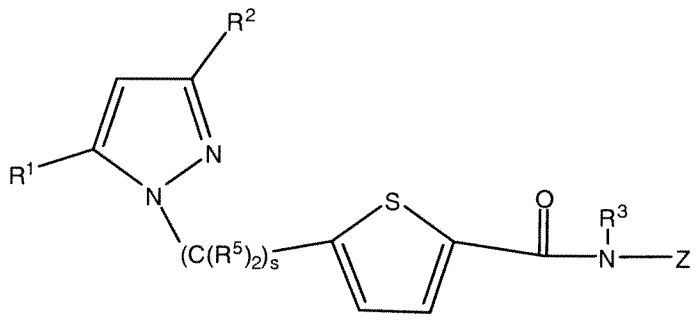
In one embodiment, in Formula (V), Z is selected from the group consisting of -(CH_2)-$(CH(CH_3))$-C(O)OH, -(CH_2)-(CH_2)-(CH_2)-C(O)OH, -(CH_2)-$C(CH_3)_2$-C(O)OH, -(CH_2)-$C(CH_3)$(OH)-C(O)OH, -CH_2-CH_2-C(O)OH, -CH_2-CH(OH)-C(O)OH, -$CH(CH_3)$-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -$CH(CH_3)$-CF_2-C(O)OH, and -CH_2-CH_2-CF_2-C(O)OH.

In one embodiment, in Formula (V), Z is  .

In one embodiment, in Formula (V), Z is  .

In one embodiment, the present invention provides a compound, or a pharmaceutically acceptable salt, solvate, ester, prodrug, tautomer, or isomer of

said compound, said compound having the general structure shown in Formula (VI):



(VI)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

R^1 is selected from the group consisting of:

phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 3 groups each independently selected from:

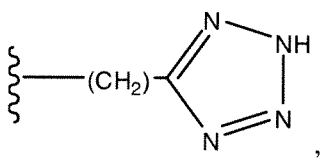
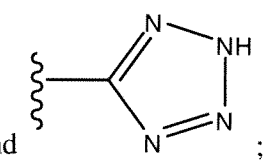
halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl;

R^2 is selected from the group consisting of:

phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 3 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl;

Z is selected from the group consisting of $-(CH_2)-(CH(CH_3))-C(O)OH$, $-(CH_2)-(CH_2)-(CH_2)-C(O)OH$, $-(CH_2)-C(CH_3)_2-C(O)OH$, $-(CH_2)-C(CH_3)(OH)-C(O)OH$, $-CH_2-CH_2-C(O)OH$, $-CH_2-CH(OH)-C(O)OH$, $-CH(CH_3)-CH_2-C(O)OH$, $-CH_2-CH(F)-C(O)OH$, $-CH_2-CF_2-C(O)OH$, $-CH(CH_3)-CF_2-C(O)OH$, $-CH_2-CH_2-CF_2-C(O)OH$,  , and  ;

and R^3 is selected from the group consisting of H and lower alkyl.

In one embodiment, in Formula (VI), $-(C(R^5)_2)_s-$ is selected from the group consisting of $-(C(CH_3)_2)_s-$, $-(CH(CH_3))_s-$, and $-(CH_2)_s-$, wherein s is 1-3.

In one embodiment, in Formula (VI), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1-2.

In one embodiment, in Formula (VI), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(C(CH_3)_2)_s$ -, -$(CH(CH_3))_s$-, and –$(CH_2)_s$-, wherein s is 1.

In one embodiment, in Formula (VI), -$(C(R^5)_2)_s$- is selected from the group consisting of -$(CH(CH_3))_s$- and –$(CH_2)_s$-, wherein s is 1.

In one embodiment, in Formula (VI), -$(C(R^5)_2)_s$- is -$(CH(CH_3))$-.

In one embodiment, in Formula (VI):

R^1 is selected from phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is selected from the group consisting of:

phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

In one embodiment, in Formula (VI):

one of R^1 and R^2 is phenyl and the other is naphthyl,

wherein each of said phenyl and said naphthyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

In one embodiment, in Formula (VI):

R^1 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is naphthyl,

wherein said naphthyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

In one embodiment, in Formula (VI):

R^1 is naphthyl,

wherein said naphthyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

In one embodiment, in Formula (VI):

R^1 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

In one embodiment, in Formula (VI), R^3 is H.

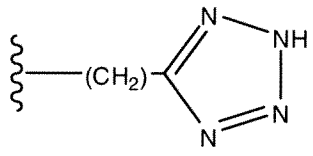
In one embodiment, in Formula (VI), R^3 is alkyl.

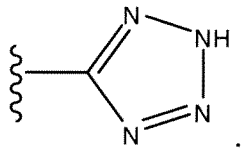
In one embodiment, in Formula (VI), R^3 is methyl.

In one embodiment, in Formula (VI), Z is selected from the group consisting of $-(CH_2)-(CH(CH_3))-C(O)OH$, $-(CH_2)-(CH_2)-(CH_2)-C(O)OH$, $-(CH_2)-C(CH_3)_2-C(O)OH$, $-(CH_2)-C(CH_3)(OH)-C(O)OH$, $-CH_2-CH_2-C(O)OH$, $-CH_2-CH(OH)-C(O)OH$, $-CH(CH_3)-CH_2-C(O)OH$, $-CH_2-CH(F)-C(O)OH$, $-CH_2-CF_2-C(O)OH$, $-CH(CH_3)-CF_2-C(O)OH$, and $-CH_2-CH_2-CF_2-C(O)OH$.

In one embodiment, in Formula (VI), R^3 is H and Z is selected from the group consisting of $-(CH_2)-(CH(CH_3))-C(O)OH$, $-(CH_2)-(CH_2)-(CH_2)-C(O)OH$, $-(CH_2)-C(CH_3)_2-C(O)OH$, $-(CH_2)-C(CH_3)(OH)-C(O)OH$, $-CH_2-CH_2-C(O)OH$, $-CH_2-$

CH(OH)-C(O)OH, -CH(CH_3)-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -CH(CH_3)-CF_2-C(O)OH, and -CH_2-CH_2-CF_2-C(O)OH.

In one embodiment, in Formula (VI), Z is  .

In one embodiment, in Formula (VI), Z is  .

In the various embodiments described herein, variables of each of the general formulas not explicitly defined in the context of the respective formula are as defined in Formula (A).

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names and chemical structures may be used interchangeably to describe that same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portion of "hydroxyalkyl", "haloalkyl", arylalkyl-, alkylaryl-, "alkoxy" etc.

"Mammal" means humans and other mammalian animals.

A "patient" is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a non-human mammal, including, but not limited to, a monkey, baboon, mouse, rat, horse, dog, cat or rabbit. In another embodiment, a patient is a companion animal, including but not limited to a dog, cat, rabbit, horse or ferret. In one embodiment, a patient is a dog. In another embodiment, a patient is a cat.

The term "obesity" as used herein, refers to a patient being overweight and having a body mass index (BMI) of 25 or greater. In one embodiment, an obese patient has a BMI of 25 or greater. In another embodiment, an obese patient has a BMI from 25 to 30. In another embodiment, an obese patient has a

BMI greater than 30. In still another embodiment, an obese patient has a BMI greater than 40.

The term "impaired glucose tolerance" (IGT) as used herein, is defined as a two-hour glucose level of 140 to 199 mg per dL (7.8 to 11.0 mmol) as measured using the 75-g oral glucose tolerance test. A patient is said to be under the condition of impaired glucose tolerance when he/she has an intermediately raised glucose level after 2 hours, wherein the level is less than would qualify for type 2 diabetes mellitus.

The term "impaired fasting glucose" (IFG) as used herein, is defined as a fasting plasma glucose level of 100 to 125 mg/dL; normal fasting glucose values are below 100 mg per dL.

The term "effective amount" as used herein, refers to an amount of Compound of Formula (I) and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a patient suffering from a Condition. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being as described herein or independently selected from the group consisting of halo, alkyl, haloalkyl, spirocycloalkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, -O-C(O)-alkyl, -O-C(O)-aryl, -O-

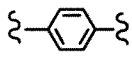
C(O)-cycloalkyl, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

The term "haloalkyl" as used herein, refers to an alkyl group, as defined above, wherein one or more of the alkyl group's hydrogen atoms have been independently replaced with –F, -Cl, -Br or –I. Non-limiting illustrative examples of haloalkyl groups include $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, and $-CH_2CHCl_2$.

"Heteroalkyl" means an alkyl moiety as defined above, having one or more carbon atoms, for example one, two or three carbon atoms, replaced with one or more heteroatoms, which may be the same or different, where the point of attachment to the remainder of the molecule is through a carbon atom of the heteroalkyl radical. Suitable such heteroatoms include O, S, S(O), $S(O)_2$, and -NH-, -N(alkyl)-. Non-limiting examples include ethers, thioethers, amines, hydroxymethyl, 3-hydroxypropyl, 1,2-dihydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-dimethylaminoethyl, and the like. The bond to the parent moiety may be through either an available carbon or heteroatom.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, *n*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene. Further non-limiting examples of alkylene groups include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$ and $-CH_2CH(CH_3)CH_2-$. In one

embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear. More generally, the suffix "ene" on alkyl, aryl, hetercycloalkyl, etc. indicates a divalent moiety, e.g., $-CH_2CH_2-$ is ethylene, and  is para-phenylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

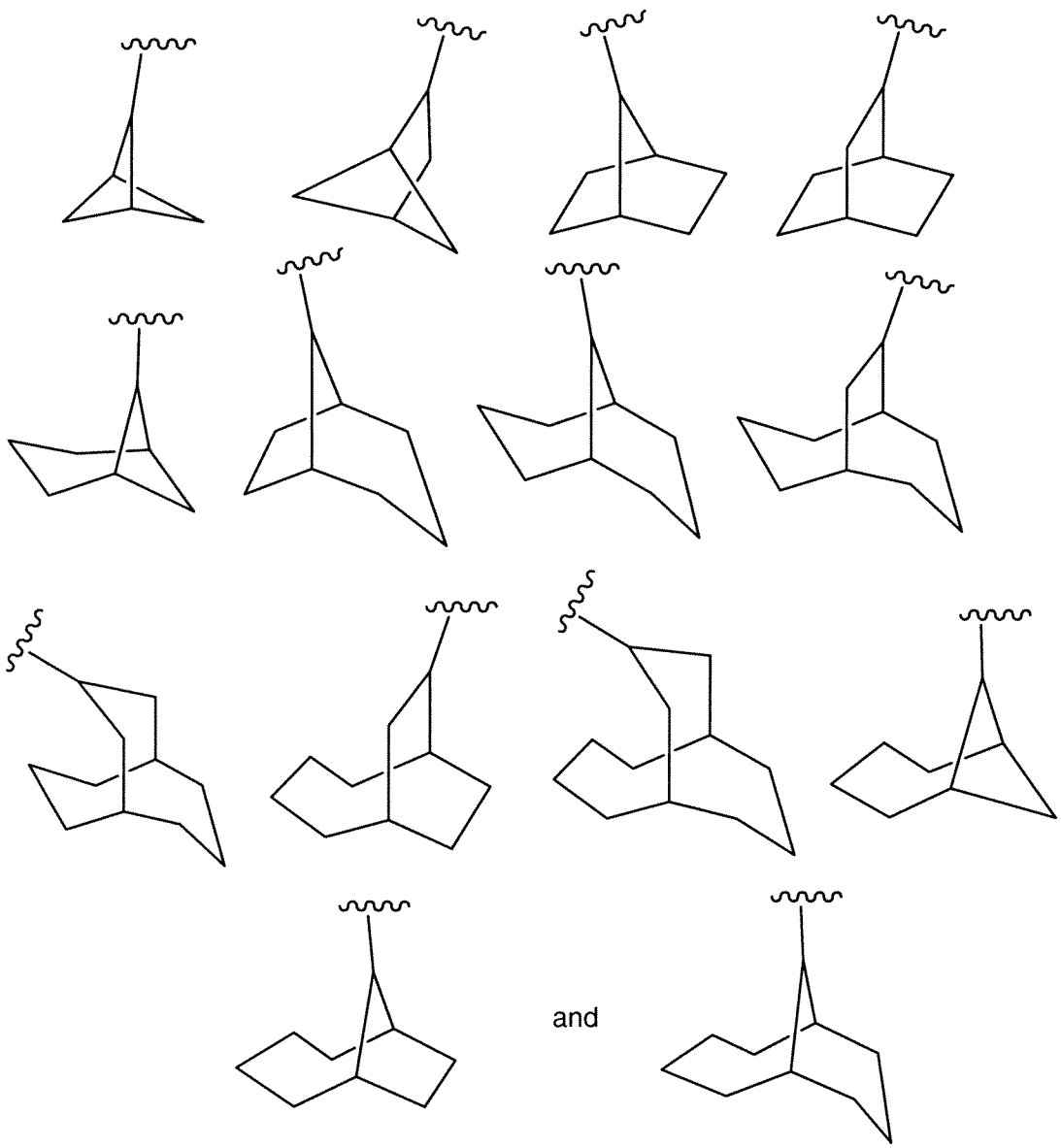
"Alkenylene" means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include –CH=CH-, $-C(CH_3)=CH-$, and $-CH=CHCH_2-$.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur

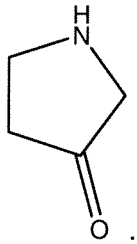
atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. The bond to the parent moiety may be through an available carbon or nitrogen atom.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following:



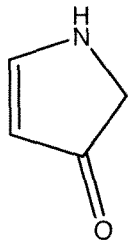
"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Heterocycloalkyl" (or "heterocyclyl") means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH- in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc)-, -N(CBz)-, -N(Tos)- group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Thus, the term "oxide," when it appears in a definition of a variable in a general structure described herein, refers to the corresponding N-oxide, S-oxide, or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Such =O groups may be referred to herein as "oxo." Example of such moiety is pyrrolidinone (or pyrrolidone):



"Heterocycloalkenyl" (or "heterocyclenyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-

carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Example of such moiety is pyrrolidenone (or pyrrolone):



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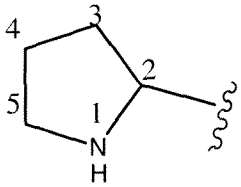
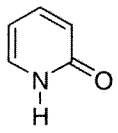
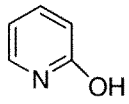
It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



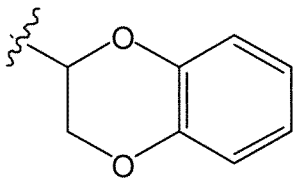
and


are considered equivalent in certain embodiments of this invention.

It should be understood that for hetero-containing functional groups described herein, e.g., heterocycloalkyl, heterocycloalkenyl, heteroalkyl, heteroaryl, and arylheterocycloalkyl (e.g., benzo-fused heterocycloalkyl), the bond to the parent moiety can be through an available carbon or heteroatom (e.g., nitrogen atom).

"Arylcycloalkyl" (or "arylfused cycloalkyl") means a group derived from a fused aryl and cycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted as described herein. Non-limiting examples of suitable arylcycloalkyls include indanyl (a benzofused cycloalkyl) and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylheterocycloalkyl" (or "arylfused heterocycloalkyl") means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylheterocycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and heterocycloalkyl consists of about 5 to about 6 ring atoms. The arylheterocycloalkyl can be optionally substituted, and/or contain the oxide or oxo, as described herein. Non-limiting examples of suitable arylfused heterocycloalkyls include:



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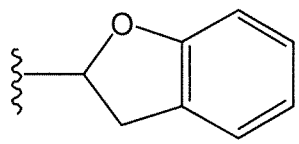

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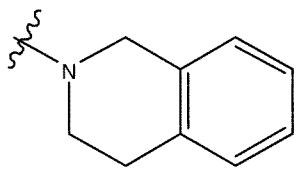

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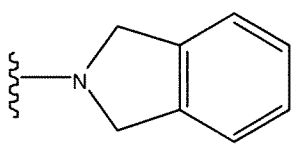

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The bond to the parent moiety is through a non-aromatic carbon or nitrogen atom atom.

It is also understood that the terms "arylfused aryl", "arylfused cycloalkyl", "arylfused cycloalkenyl", "arylfused heterocycloalkyl", arylfused heterocycloalkenyl", "arylfused heteroaryl", "cycloalkylfused aryl", "cycloalkylfused cycloalkyl", "cycloalkylfused cycloalkenyl", "cycloalkylfused heterocycloalkyl", "cycloalkylfused heterocycloalkenyl", "cycloalkylfused heteroaryl, "cycloalkenylfused aryl", "cycloalkenylfused cycloalkyl", "cycloalkenylfused cycloalkenyl", "cycloalkenylfused heterocycloalkyl", "cycloalkenylfused heterocycloalkenyl", "cycloalkenylfused heteroaryl", "heterocycloalkylfused aryl", "heterocycloalkylfused cycloalkyl", "heterocycloalkylfused cycloalkenyl", "heterocycloalkylfused heterocycloalkyl", "heterocycloalkylfused heterocycloalkenyl", "heterocycloalkylfused heteroaryl", "heterocycloalkenylfused aryl", "heterocycloalkenylfused cycloalkyl", "heterocycloalkenylfused cycloalkenyl", "heterocycloalkenylfused heterocycloalkyl", "heterocycloalkenylfused heterocycloalkenyl", "heterocycloalkenylfused heteroaryl", "heteroarylfused aryl", "heteroarylfused cycloalkyl", "heteroarylfused cycloalkenyl", "heteroarylfused heterocycloalkyl", "heteroarylfused heterocycloalkenyl", and "heteroarylfused heteroaryl" are similarly represented by the combination of the groups aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, as previously described. Any such groups may be unsubstituted or substituted with one or more ring system substituents at any available position as described herein.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl. The term (and similar terms) may be written as "arylalkyl-" to indicate the point of attachment to the parent moiety.

Similarly, "heteroarylalkyl", "cycloalkylalkyl", "cycloalkenylalkyl", "heterocycloalkylalkyl", "heterocycloalkenylalkyl", etc., mean a heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, etc. as described herein bound to a parent moiety through an alkyl group. Preferred groups

contain a lower alkyl group. Such alkyl groups may be straight or branched, unsubstituted and/or substituted as described herein.

Similarly, "arylfused arylalkyl-", arylfused cycloalkylalkyl-, etc., means an arylfused aryl group, arylfused cycloalkyl group, etc. linked to a parent moiety through an alkyl group. Preferred groups contain a lower alkyl group. Such alkyl groups may be straight or branched, unsubstituted and/or substituted as described herein.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl, adamantylpropyl, and the like.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclylalkyl" (or "heterocycloalkylalkyl") means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Cyanoalkyl" means a NC-alkyl- group in which alkyl is as previously defined. Preferred cyanoalkyls contain lower alkyl. Non-limiting examples of suitable cyanoalkyl groups include cyanomethyl and 2-cyanoethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl carbon. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl carbon. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Heteroaroyl" means an heteroaryl-C(O)- group in which the heteroaryl group is as previously described. The bond to the parent moiety is through the carbonyl carbon. Non-limiting examples of suitable groups include pyridoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. The bond to the parent moiety is through the ether oxygen.

"Alkyoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" (or "arylalkyloxy") means an aralkyl-O- group (an arylaklyl-O- group) in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from a aryl and alkenyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl carbon.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl carbon.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl carbon.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfur atom of the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfur atom of the sulfonyl.

"Spriocycloalkyl" means a cycloalkyl group attached to a parent moiety at a single carbon atom. Non-limiting examples of spirocycloalkyl wherein the parent moiety is a cycloalkyl include spiro [2.5] octane, spiro [2.4] heptane, etc. Non-limiting examples of spriocycloalkyl wherein the parent moiety is an The alkyl moiety linking fused ring systems (such as the alkyl moiety in heteroarylfused heteroarylalkyl-) may optionally be substituted with spirocycloalkyl or other groups as described herein. Non-limiting spirocycloalkyl groups include spirocyclopropyl, spriorcyclobutyl, spirocycloheptyl, and spirocyclohexyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylfused cycloalkylalkyl- moiety or the like includes substitution on any ring portion and/or on the alkyl portion of the group.

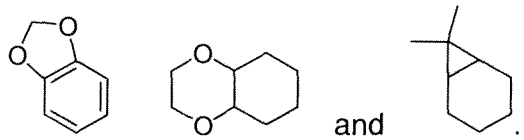
When a variable appears more than once in a group, e.g., R^8 in $-N(R^8)_2$, or a variable appears more than once in a structure presented herein such as Formula (I), the variables can be the same or different.

The term, "compound(s) of the invention," as used herein, refers, collectively or independently, to any of the compounds embraced by the general formulas described herein, e.g., Formula (A), Formula (I), Formula (II-A), Formula (II-B), Formula (II-B1), Formula (II-B2), Formula (II-B3), Formula (II-B4), Formula (II-B5), Formula (II-C), Formula (II-C1), Formula (II-C2), Formula (II-C3), Formula (II-C4), Formula (II-C5), Formula (II-D), Formula (II-D1), Formula (II-D2), Formula (III), Formula (IV), Formula (IV), Formula (V), and Formula (VI), and the example compounds thereof.

With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. With respect to the compositions and methods comprising the use of "at least one compound of the invention, e.g., of Formula (I)," one to three compounds of the invention, e.g., of Formula (I) can be administered at the same time, preferably one.

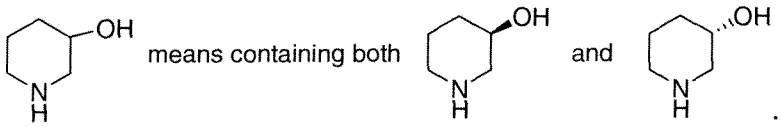
Compounds of the invention may contain one or more rings having one or more ring system substituents. "Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being as described herein or independently selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moieties are rings such as

heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl rings. Additional non-limiting examples include methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:

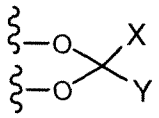


As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The line ----,as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example:



The wavy line ∿∿∿, as used herein, indicates a point of attachment to the rest of the compound. For example, each wavy line in the following structure:



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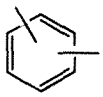
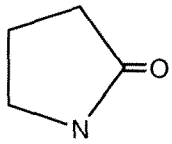
indicates a point of attachment to the core structure, as described herein.

Lines drawn into the ring systems, such as, for example:



indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

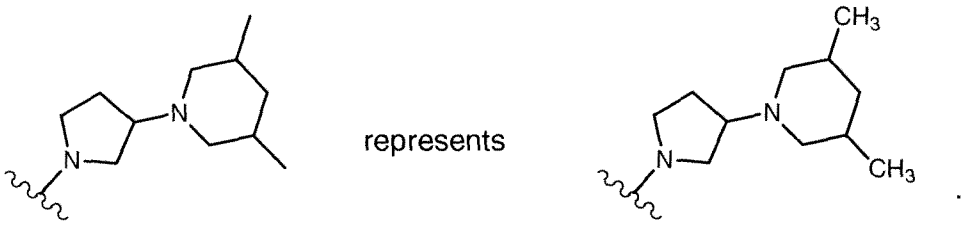
"Oxo" is defined as a oxygen atom that is double bonded to a ring carbon in a cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, or other ring described herein, e.g.,



In this specification, where there are multiple oxygen and/or sulfur atoms in a ring system, there cannot be any adjacent oxygen and/or sulfur present in said ring system.

It is noted that the carbon atoms for compounds of the invention may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



In one embodiment, a compound or compounds of the invention is/are in isolated or purified form.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like) , in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the

protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1999), Wiley, New York.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl

(such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of the invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of the invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates,

methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al, J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al, AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al, Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of the invention can form salts which are also within the scope of this invention. Reference to a compound of the invention herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of the invention contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the invention may be formed, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl),

aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of the invention, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

The compounds of the invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of the invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

It is also possible that the compounds of the invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of the invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of the invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased

in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Suitable hydrogen atoms of the compounds of the invention which may be deuterated include, in each of Formula (A), Formula (I), Formula (III), Formula (IV), Formula (V), and/or Formula (VI), one or more hydrogen atoms of the lower alkyl group(s) and/or hydroxyl-substituted lower alkyl groups of R^5. A non-limiting example of such deuterated compounds include the compound of Example 22, below.

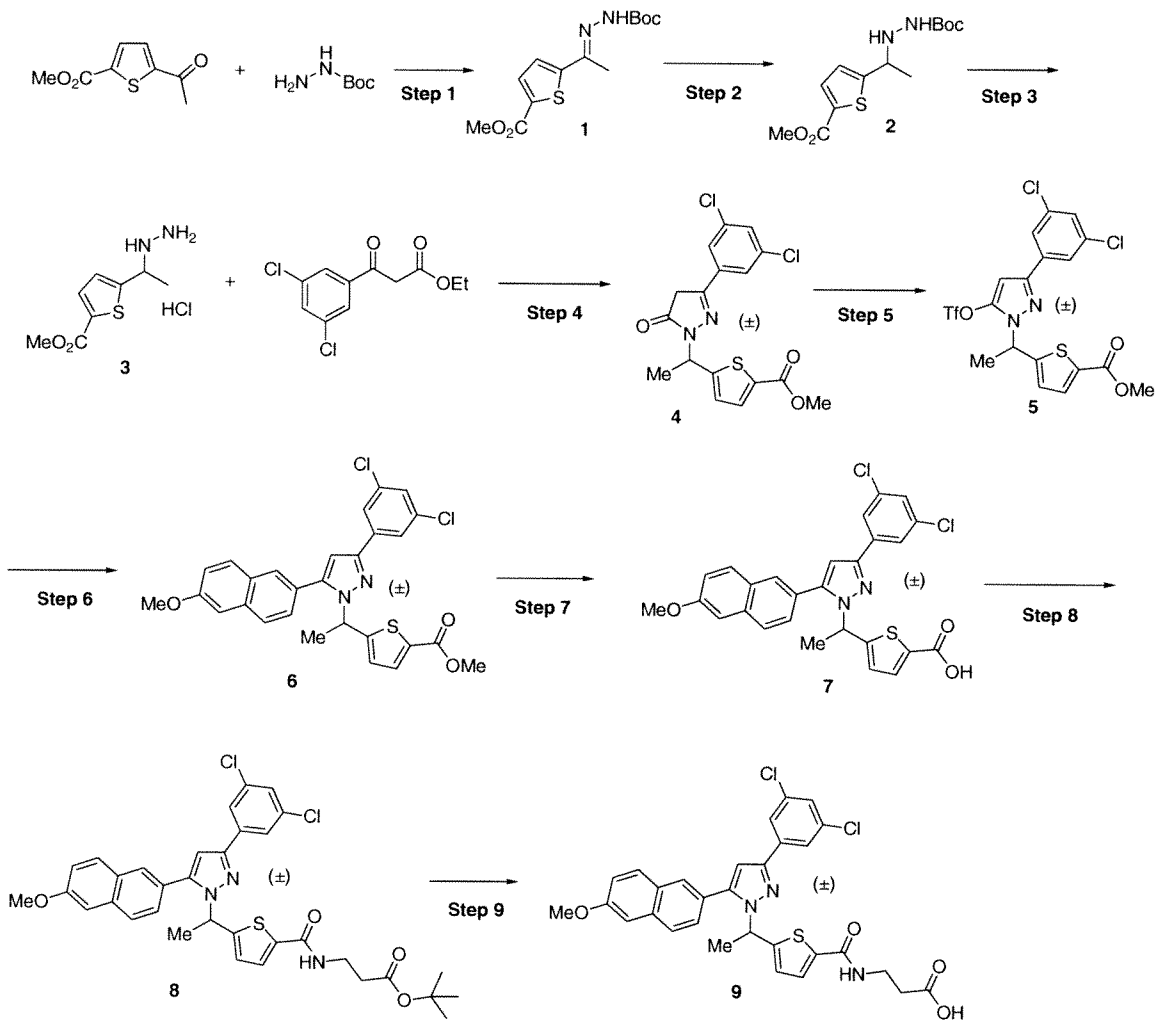
Additional suitable hydrogen atoms which may be deuterated include, in each of Formula (A), Formula (I), Formula (III), Formula (IV), Formula (V), and/or Formula (VI), one or more hydrogen atoms of the groups R^{11}, R^{12} and/or R^{13} of Z. A non-limiting example of such deuterated compounds include the compound of Example 27, below.

Additional suitable hydrogen atoms which may be deuterated include, in each of Formula (A), Formula (I), Formula (III), Formula (IV), Formula (V), and/or Formula (VI), one or more hydrogen atoms of R^1 and/or R^2. For example, when R^1 (or R^2) is phenyl or naphthyl, one or more available hydrogen atoms bound to said phenyl and/or said naphthyl group may be replaced by deuterated hydrogen. A non-limiting example of such deuterated compounds include the compound of Example 28, below.

Polymorphic forms of the compounds of the invention, and of the salts, solvates, esters and prodrugs of the compounds of the invention, are intended to be included in the present invention.

EXAMPLES

Scheme 1



Step 1 To the thiophene (1.0 g, 5.4 mmol) in THF (12 mL) at room temperature was added *tert*-butylcarbazate (0.72 g, 5.4 mmol). The reaction mixture was stirred at room temperature for 18 h and then concentrated *in vacuo* to provide the hydrazone **1** (1.6 g, 100%).

Step 2 To the hydrazone **1** (1.2 g, 3.95 mmol) in THF (9 mL) at room temperature was added acetic acid (3 mL) and sodium cyanoborohydride (0.37 g, 5.9 mmol). The reaction was stirred at room temperature for 18 h. Added 1 N NaOH (excess) and stirred the mixture for 5 minutes. The mixture was then extracted with DCM. The combined DCM extracts wer washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatoghraphy (0-25% EtOAc/hex over 30 minutes) to provide the hydrazine **2** (0.78 g, 2.6 mmol).

Step 3 To the hydrazine **2** (0.78 g, 2.6 mmol) in DCM (10 mL) at room temperature was added 2N HCl/Ether (15 mL). The reaction was stirred at room temperature for 18 h. The mixture was then concentrated *in vacuo* to provide **3** (0.75 g).

Step 4 To the hydrazine **3** (0.2 g, 0.84 mmol) in MeOH (3 mL) was added ethyl-3,5-dichlorobenzoylformate (Oakwood Products, Inc.) (0.22 g, 0.84 mmol). The mixture was heated to reflux and stirred for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was purifed by silica gel chromatography (0-30% EtOAc/hex over 25 min.) to provide **4** (0.12 g, 0.3 mmol).

Step 5 To **4** (0.11 g, 0.28 mmol) in THF (2 mL) at -78 C was TEA (0.19 mL) followed by trifluoromethanesulfonic anhydride (0.09 mL, 0.56 mmol). The cold bath was removed and the reaction stirred for 18 h. To the reaction was added EtOAc. The mixture was washed with 1N HCl, water, and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hex over 30 minutes) to provide the triflate **5** (0.11 g, 0.21 mmol).

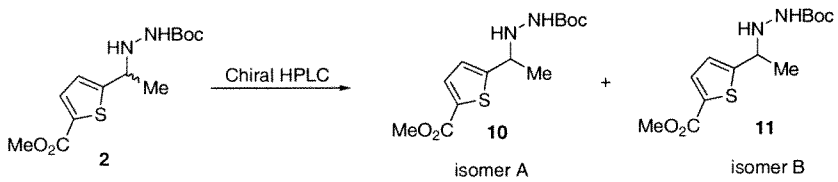
Step 6 To the triflate **5** (0.11 g, 0.21 mmol) in dimethoxyethane (2 mL) was added 6-methoxy-2-naphthyl boronic acid (0.06 g, 0.3 mmol) and TEA (0.06 mL, 0.42 mmol). The reaction was purged with N_2 gas for 15 minutes. $Pd(PPh_3)_4$ (0.019 g, 0.017 mmol) was added and the reaction was sealed and heated in a microwave reactor to 100 C for 15 minutes. The reaction mixture was taken up into EtOAc and washed with 1N HCl, saturated NH_4Cl, water, and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-15% EtOAc/hex over 30 minutes) to provide a residue that was repurified by preparative TLC (SiO_2-2000 μ, 15% EtOAc/hex) to yield **6** (0.058 g, 0.10 mmol).

Step 7 To **6** (0.05 g, 0.09 mmol) in THF (0.5 mL) at room temperature was added 2N LiOH (0.45 mL). After 18 h at room temperature, another aliquot of 2N LiOH (0.45 mL) was added. The reaction was stirred for an additional 18 h. The mixture made acidic with aqueous 1N HCl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **7** (0.05 g).

Step 8 To **7** (0.043 g, 0.08 mmol) in DMF (1 mL) was added diisopropylethyl amine (0.057 mL, 0.33 mmol), β-alanine *tert*-butyl ester hydrochloride (0.03 g, 0.16 mmol) and PyBOP (0.05 g, 0.1 mmol). The reaction was stirred at room temperature for 18 h. Water was added and the reaction was extracted with EtOAc. The organic layer was washed with 1N HCl, water, and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO_2-1000 μ, 35% EtOAc/hex) to provide **8** (0.042 g).

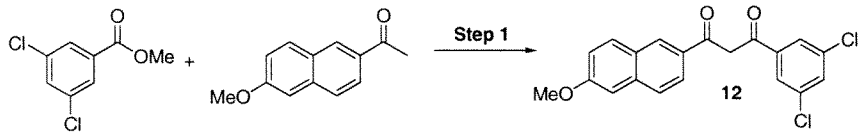
Step 9 To **8** (0.036 g) in DCM (0.5 mL) was added TFA (0.5 mL). The solution was stirred at room temperature for 2 h. The reaction was concentrated *in vacuo* to provide **9**.

Scheme 2



The enantiomers of racemic **2** were separated by chiral HPLC [Chiralcel OD 5% IPA/hexanes, isomer A retention time = 19.5 minutes, Isomer B retention time = 21.9 minutes] to provide isomer A **10** and isomer B **11**.

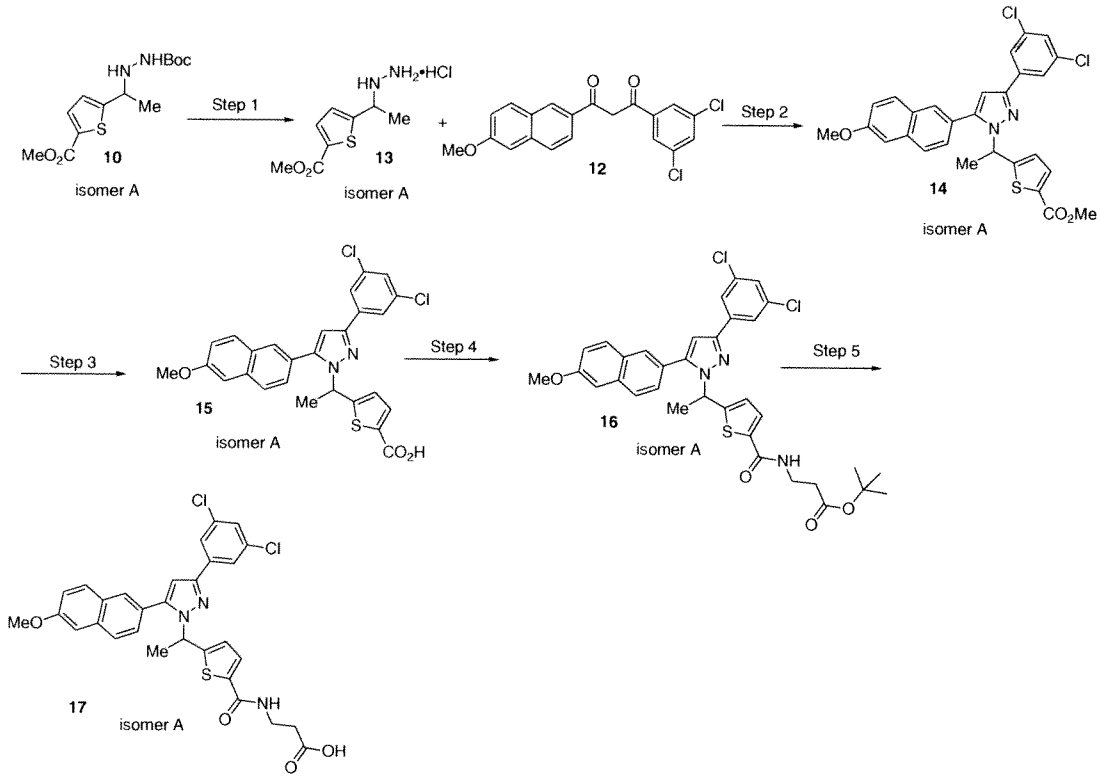
Scheme 3



Step 1

To 3,5-dichlorobenzoic acid methyl ester (10.4 g, 50.5 mmol) in THF (170 mL) was added 2-acetyl-6-methoxynaphthalene (12.6 g, 63.1 mmol) and NaH (60% dispersion in mineral oil, 7.3 g, 120 mmol). Warmed to reflux and stirred for 18 h. Cooled to 0 C added 4N HCl very slowly (Gas evolution). Extracted the mixture with EtOAc. Combined the organics and washed with water and brine. Dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Recrystallized the solid with hot ethyl acetate/hexane to provide **12** (11.9 g, 31.9 mmol).

Scheme 4



Step 1

To **10** (1.44 g, 4.8 mmol) in DCM (15 mL) and methanol was added 2N HCl/ether (50 mL). After 18 h, the mixture was concentrated *in vacuo* to provide **13** as a white solid (1.15 g, 4.8 mmol).

Step 2

To **13** (0.36 g, 1.5 mmol) in dimethylacetamide (6 mL) was added **12** (0.47 g, 1.25 mmol) and tetrabutylammonium chloride (0.35 g, 1.25 mmol). The mixture was warmed to 65 C and stirred for 18 h. The reaction was cooled to room temperature and then added to water. The mixture was extracted with EtOAc. The combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hex) to provide **14** (0.38 g, 0.70 mmol).

Step 3

To **14** (0.36 g, 0.68 mmol) in THF (4 mL) was added aqueous 2N LiOH (10 mL). The mixture was warmed to 40 C and stirred for 12 h. The reaction was cooled to room temperature and acidified with 1N HCl. The mixture was extracted with

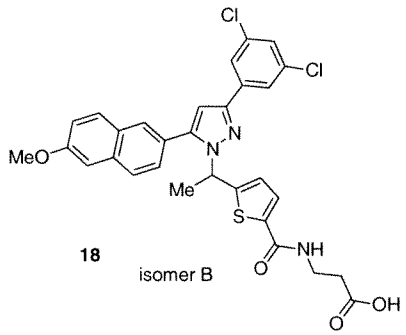
EtOAc. The combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **15** (0.36 g, 0.68 mmol).

Step 4

To **15** (0.08 g, 0.15 mmol) in DMF (1 mL) was added β-alanine *tert*-butyl ester hydrochloride (0.055 g, 0.31 mmol), diisopropylethyl amine (0.11 mL, 0.61 mmol), and PyBoP (0.095 g, 0.18 mmol). Stirred the reaction at room temperature for 18 h. The reaction was taken up into EtOAc and washed with 1N HCl, 1N NaOH, water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (2000 μ SiO_2, 35% EtOAc/hex) to provide **16** (0.076 g, 0.12 mmol).

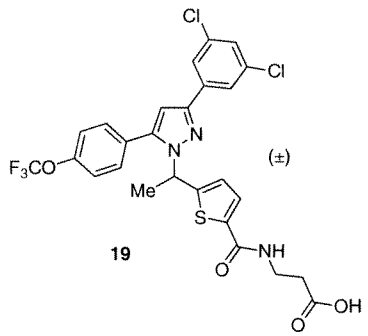
Step 5

To **16** (0.076 g, 0.12 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 1 h and then concentrated *in vacuo* to provide **17** (0.063 g, 0.11 mmol).



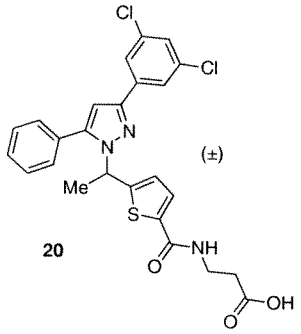
18
isomer B

Isomer B (**18**) was prepared in a similar fashion as isomer A (**17**) in Scheme 4 except that thiophene **11** was used instead of thiophene **10** in step 1.



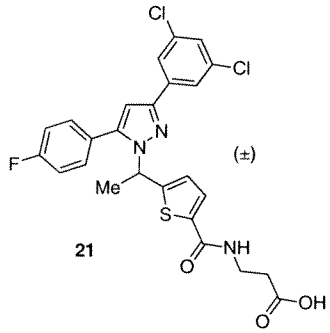
19

Compound **19** was prepared in the same manner as **9** in Scheme 1 except that 4-trifluoromethoxyphenyl boronic acid was used instead of 6-methoxy-2-naphthyl boronic acid in step 6.



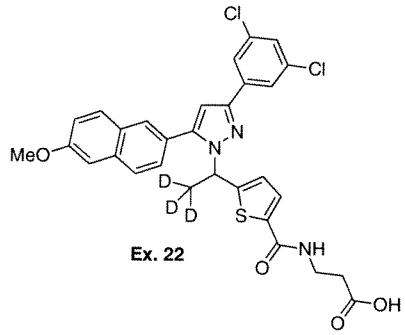
20

Compound **20** was prepared in the same manner as **9** in Scheme 1 except that phenyl boronic acid was used instead of 6-methoxy-2-naphthyl boronic acid in step 6.



21

Compound **21** was prepared in the same manner as **9** in Scheme 1 except that 4-fluorophenyl boronic acid was used instead of 6-methoxy-2-naphthyl boronic acid in step 6.



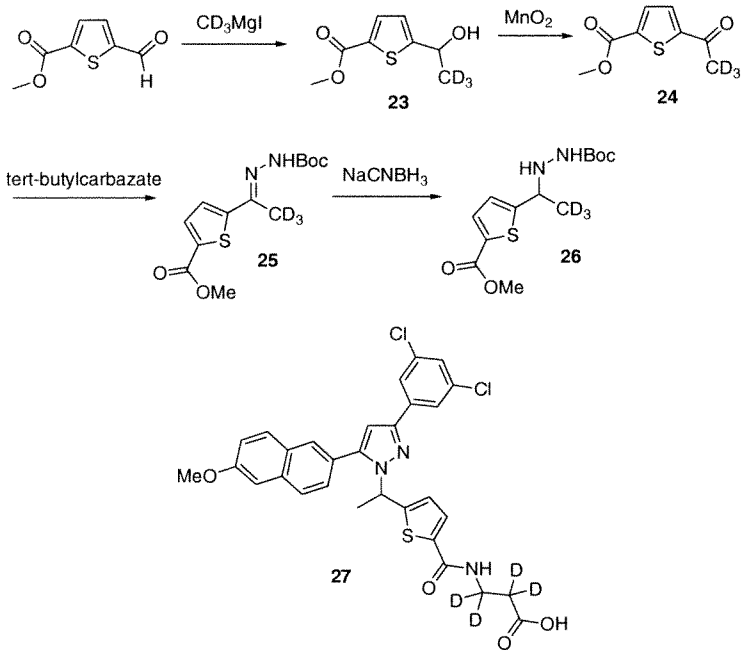
Ex. 22

As described above, deuterated analogs of the compounds of the invention are also contemplated as being within the scope of the present

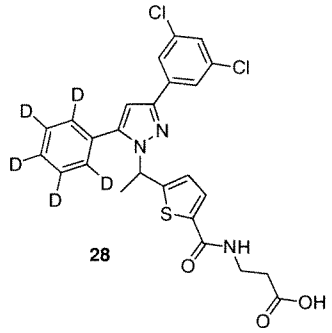
invention. Non-limiting examples include the compounds of Examples 22, 27, and 28.

The deuterated **Ex. 22** could be prepared by first preparing the deuterated analog of **2**. This can be prepared as shown in scheme 5. Ex. X can then be prepared by using **26** instead of **2** in Scheme 1. Non-racemic analogs could also be prepared using chemistry described in Scheme 2 and Scheme 3 when **26** is used instead of **2**.

Scheme 5



The deuterated analog **Ex. 27** could be prepared by using a protected beta-alanine-2,2,3,3-D4 in step 8 of scheme 1 or step 4 of scheme 2. Beta-alanine-2,2,3,3-D4 is commercially available from C/D/N Isotopes Inc.



The deuterated analog **Ex. 28** could be prepared by using phenyl-D5-boronic acid (available from Aldrich) in step 6 of scheme 1 instead of 6-methoxy-2-naphthyl boronic acid.

Microwave Reactions

All microwave reactions were performed using a Biotage Initiator Sixty microwave reactor.

Analytical Chromatography Conditions

The conditions utilized for the Electro Spray Ionization Liquid Chromatography-Mass Spectrometry (ESI-LC/MS) analysis of all examples described is as follows:

Column:	Phenomenex Gemini C-18, 50 x 4.6 mm, 5 micron.
Mobile phase:	A: 0.05% Trifluoacetic acid in water
	B: 0.05% Trifluoacetic acid in acetonitrile
Gradient:	90% A and 10% B to 5% A and 95% B over 5 minutes
Flow rate:	1.0 mL/min
UV detection:	254 nm
Spectrometer:	PE SCIEX API-150EX, single quadrupole mass spectrometer.

High Resolution Mass Spectrometry Conditions

The conditions utilized for the High Resolution Mass Spectrometry (HRMS) analysis of all examples described is as follows:

Mobile phase:	A: 0.1% Trifluoacetic acid in water
	B: 0.1% Trifluoacetic acid in acetonitrile
Elution:	Isocratic, 5% A and 95% B
Flow rate:	0.1 mL/min
Method:	direct infusion with NaCsI external standard calibrant.
HPLC System:	Agilent 1110
Spectrometer:	JEOL Accu-ToF model: JMS-T110LC

Preparative Chromatography Conditions

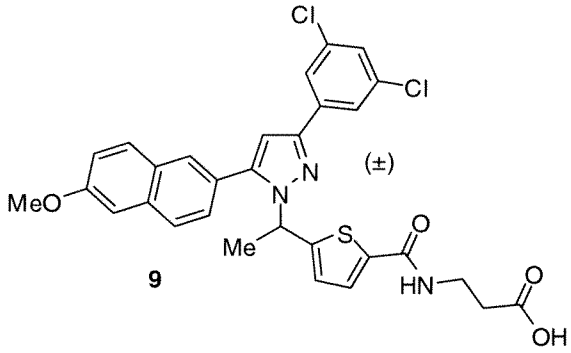
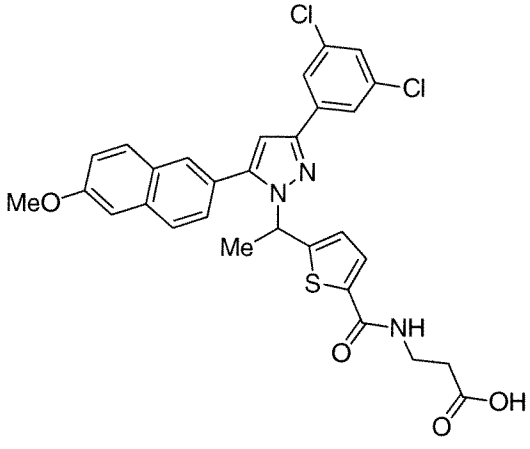
The conditions utilized for Preparative C18 Reversed-Phase Liquid Chromatography purification is as follows:

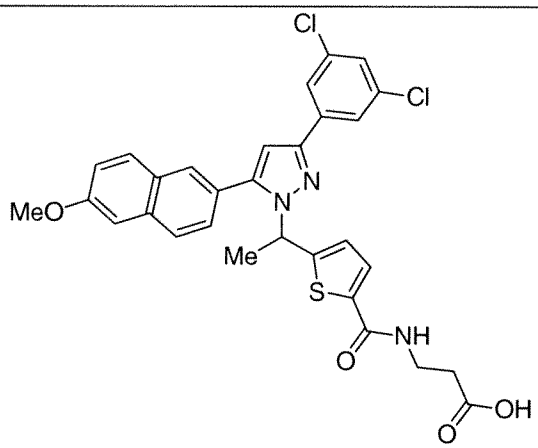
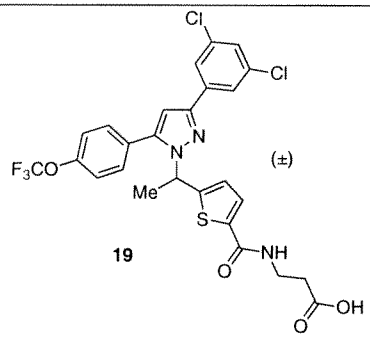
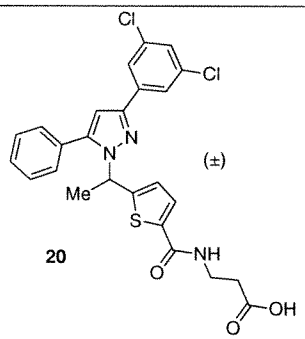
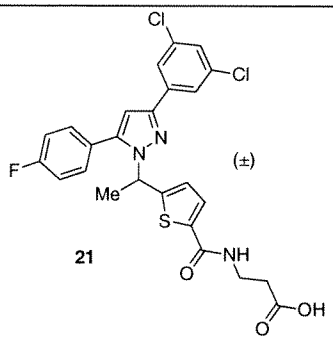
Column:	Waters Prep LC 25mm Module.
	25mm x 100mm Nova Pak® HR, C18, 6μm, 60 Å column.
Mobile phase:	A: 0.1% formic acid in water
	B: 0.1% formic acid in acetonitrile
Elution:	Hold at 90% A and 10% B for 1 minute
	Gradient from 10% B to 100% B over 10 minutes

Hold at 100% B for 6 minutes
Flow rate: 30 mL/min
UV detection: 254 nm

Example Compounds of the Invention

Table A: The compounds of the invention shown in the following table (Table A) can be prepared according to one or more of the methods reported above. The observed ESI-LC/MS [M+H] is the observed mass spectrometryr reading for the compound indicated. The retention time value refers to the retention time (in minutes) of the compound indicated when subjected to the LCMS conditions described above. The observed High Resolution Mass Spectrometry (HRMS) reading is the observed reading (as either $[M+H]^+$ or $[M+Na]^+$) for the compound indicated when subjected to the HRMS conditions described above. "--" in the table below means not measured.

Example	Compound	ESI-LC/MS [M+H}	Retention Time (min)	HRMS
9	 **9**	594.3	5.64	--
17, Isomer A non-racemic		594.3	5.64	--

Example	Compound	ESI-LC/MS [M+H}	Retention Time (min)	HRMS
18, Isomer B non-racemic		594.3	5.64	--
19		598.3	5.52	
20		514.3	5.20	
21		532.3	5.21	

Abbreviation List:

Abbreviation	Reagent
EDCI	1,3-Propanediamine, N3-(ethylcarbonimidoyl)-N1,N1-dimethyl-, hydrochloride
iPr_2NEt	diisopropylethylamine
HOBt	1-hydroxybenzotriazole
MeCN	acetonitrile
Et_2O	diethyl ether
$Cu(OAc)_2$	copper (II) acetate
EtOH	ethanol
DCE	1,2-dichloroethane
DMF	*N,N*-dimethylformamide
MeOH	methanol
PyBOP	benzotriazol-1-yloxy tris(pyrrolidino)phosphonium hexafluorophosphate
DMF·DMA	*N,N*-dimethylformamide, dimethyl acetal
THF	tetrahydrofuran
TFA	trifluoroacetic acid
$Pd/BaSO_4$	palladium on barium sulfate
LDA	lithium diisopropylamide
NaOH	sodium hydroxide
EtOAc	ethyl acetate
Na_2SO_4	sodium sulfate
$MgSO_4$	magnesium sulfate
Et_3N	triethylamine
$Pd(OAc)_2$	palladium (II) acetate
NaOt-Bu	sodium *tert*-butoxide
X-Phos	2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl
$NaHCO_3$	sodium bicarbonate
NH_4Cl	ammonium chloride

NH_4OH	ammonium hydroxide
CCl_4	carbon tetrachloride

Biological Assays

The ability of the compounds of the invention to inhibit the binding of glucagon and their utility in treating or preventing type 2 diabetes mellitus and related conditions can be demonstrated by the following *in vitro* assays.

Glucagon Receptor Binding Assay

Recombinant human glucagon receptor (huGlucR) membranes and mouse glucagon receptor (mGlucR) membranes were prepared in-house from huGlucR/clone 103c/CHO and mouse liver tissue, respectively. 0.03ug/li huGluR membranes (or 0.5 ug/ml mGlucR) was incubated in assay buffer containing 0.05 nM ^{125}I- Glucagon (Perkin Elmer, NEX 207) and varying concentrations of antagonist at room temperature for 60 to 90 (assay buffer: 50 mM HEPES, 1mM MgCl2, 1 mM CaCl2, 1 mg/ml BSA, COMPLETE protease inhibitor cocktail, pH 7.4) . The total volume of the assay was 200 ul. The assay was performed at room temperature using 96 –deep well plate. Compound 4c, racemic diastereomer 1 (D1), (1.0 μM final concentration), described by G.H. Ladouceur et al. in Bioorganic and Medicinal Chemistry Letters, 12 (2002), 3421-3424, was used to determine non-specific binding. Following incubation, the reaction was stopped by rapid filtration through Unfilter-96 GF/C glass fiber filter plates (Perkin Elmer) pre-soaked in 0.5 % polyethyleneimine. The filtrate was washed using 50 mM Tris-HCl, pH 7.4. Dried filter plates containing bound radioactivity were counted in the presence of scintillation fluid (Microscint 0, Perkin-Elmer) using a Topcount scintillation counter. Data was analyzed using the software program Prism (GraphPad). IC_{50} values were calculated using non-linear regression analysis assuming single site competition.

Inhibition of Glucagon-Stimulated Intracellular cAMP Assay

Recombinant human glucagon receptor-expressing CHO cells were harvested using a non-enzymatic cell dissociation solution (GIBCO 2672), pelleted and resuspended in stimulation buffer (1 X HBSS, 5 mM Hepes, 0.1% BSA, pH7.4 in

the presence of proteinase inhibitor and phosphodiesterase inhibitors). The adenylate cyclase assay was constructed following the LANCE cAMP Kit (Perkin Elmer, AD0264) instructions. Briefly, cells were preincubated with anti-cAMP antibody and 12 points series diluted compound in stimulation buffer with a final concentration of 3% DMSO for 30 minutes prior to stimulation with 300 pM glucagon for 45 minutes. The reaction was stopped by incubating with the supplied detection buffer containing Europium chelate of the Eu-SA/Biotin-cAMP tracer for 20 hours. The assay was done as triplicates in a 384 well plate. Fluorescence at 665 nm was measured using PheraStar instruments. Basal activity (100% inhibition) was determined using the DMSO control and 0% inhibition was defined as cAMP stimulation produced by 300 pM glucagon. Standard cAMP concentrations were assayed concurrently for conversion of fluorescence signal to cAMP level. Data was analyzed using the software program Prism from GraphPad. IC_{50} values were calculated using non-linear regression analysis assuming single site competition. IC_{50} values for the compounds of the invention shown in the examples measured less than about 10 μM, in preferred embodiments less than about 1 μM, in more preferred embodiments less than about 500 nM.

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of the invention described above in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides a method for inhibiting glucagon receptors comprising exposing an effective amount of a compound or a composition comprising a compound of the invention to glucagon receptors. In one embodiment, said glucagon receptors are part of a glucagon receptor assay. Non –limiting examples of such assays include glucagon receptor assays and glucagon-strimuloated intracellular cAMP formation assays such as those described above. In one embodiment, said glucagon receptors are expressed in a population of cells. In one embodiment, the population of cells is in *in vitro*. In one embodiment, the population of cells is in *ex vivo*. In one embodiment, the population of cells is in a patient.

Methods of Treatment, Compositions, and Combination Therapy

In another embodiment, the present invention provides a method of treating type 2 diabetes mellitus in a patient in need of such treatment comprising administering to said patient a compound of the invention or a composition comprising a compound of the invention in an amount effective to treat type 2 diabetes mellitus.

In another embodiment, the present invention provides a method of delaying the onset of type 2 diabetes mellitus in a patient in need of such treatment comprising administering to said patient a compound of the invention or a composition comprising a compound of the invention in an amount effective to delay the onset of type 2 diabetes mellitus.

In another embodiment, the present invention provides a method of treating hyperglycemia, diabetes, or insulin resistance in a patient in need of such treatment comprising administering to said patient a compound of the invention, or a composition comprising a compound of the invention, in an amount that is effective to treat hyperglycemia, diabetes, or insulin resistance.

In another embodiment, the present invention provides a method of treating non-insulin dependent diabetes mellitus in a patient in need of such treatment comprising administering to said patient an anti-diabetic effective amount of a compound of the invention or a composition comprising an effective amount of a compound of the invention.

In another embodiment, the present invention provides a method of treating obesity in a patient in need of such treatment comprising administering to said patient a compound of the invention or a composition comprising a compound of the invention in an amount that is effective to treat obesity.

In another embodiment, the present invention provides a method of treating one or more conditions associated with Syndrome X (also known as metabolic syndrome, metabolic syndrome X, insulin resistance syndome, Reaven's syndrome) in a patient in need of such treatment comprising administering to said patient a compound of the invention or a composition comprising an effective amount of a compound of the invention in an amount that is effective to treat Syndrome X.

In another embodiment, the present invention provides a method of treating a lipid disorder in a patient in need of such treatment comprising

administering to said patient a compound of the invention, or a composition comprising a compound of the invention, in an amount that is effective to treat said lipid disorder. Non-limiting examples of such lipid disorders include: dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL and high LDL, and metabolic syndrome.

In another embodiment, the present invention provides a method of treating atherosclerosis in a patient in need of such treatment comprising administering to said patient a compound of the invention or a composition comprising a compound of the invention, in an amount effective to treat atherosclerosis.

In another embodiment, the present invention provides a method of delaying the onset of, or reducing the risk of developing, atherosclerosis in a patient in need of such treatment comprising administering to said patient a compound of the invention or a composition comprising a compound of the invention, in an amount effective to delay the onset of, or reduce the risk of developing, atherosclerosis.

In another embodiment, the present invention provides a method of treating a condition or a combination of conditions selected from hyperglycemia, low glucose tolerance, insulin resistance, obesity, abdominal obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, atherosclerosis and its sequelae, vascular restenosis, pancreatitis, neurodegenerative disease, retinopathy, nephropathy, neuropathy, Syndrome X and other conditions where insulin resistance is a component, in a patient in need thereof, comprising administering to said patient a compound of the invention, or a composition comprising a compound of the invention, in an amount that is effective to treat said condition or conditions.

In another embodiment, the present invention provides a method of delaying the onset of a condition or a combination of conditions selected from hyperglycemia, low glucose tolerance, insulin resistance, obesity, abdominal obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, atherosclerosis and its sequelae, vascular restenosis, pancreatitis, neurodegenerative disease, retinopathy, nephropathy, neuropathy, Syndrome X

and other conditions where insulin resistance is a component, in a patient in need thereof, comprising administering to said patient a compound of the invention, or a composition comprising a compound of the invention, in an amount that is effective to delay the onset said condition or conditions.

In another embodiment, the present invention provides a method of reducing the risk of developing a condition or a combination of conditions selected from hyperglycemia, low glucose tolerance, insulin resistance, obesity, abdominal obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, atherosclerosis and its sequelae, vascular restenosis, pancreatitis, neurodegenerative disease, retinopathy, nephropathy, neuropathy, Syndrome X and other conditions where insulin resistance or hyperglycemia is a component, in a patient in need thereof, comprising administering to said patient a compound of the invention, or a composition comprising a compound of the invention, in an amount that is effective to reduce the risk of developing said condition or conditions.

In another embodiment, the present invention provides a method of treating a condition selected from type 2 diabetes mellitus, hyperglycemia, low glucose tolerance, insulin resistance, obesity, abdominal obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, atherosclerosis and its sequelae, vascular restenosis, pancreatitis, neurodegenerative disease, retinopathy, nephropathy, neuropathy, Syndrome X and other conditions where insulin resistance is a component, in a patient in need thereof, comprising administering to said patient effective amounts of a compound of the invention and one or more additional active agents.

Non-limiting examples of such additional active agents include the following:

DPP-IV inhibitors. Non-limiting examples of DPP-IV inhibitors include alogliptin (Takeda), saxagliptin (Brystol-Myers Squibb), sitagliptin (Januvia™, Merck), vildagliptin (Galvus™, Novartis), denagliptin (GlaxoSmithKline), ABT-279 and ABT-341 (Abbott), ALS-2-0426 (Alantos), ARI-2243 (Arisaph), BI-A and BI-B (Boehringer Ingelheim), SYR-322 (Takeda), compounds disclosed in US Patent No. 6,699,871, MP-513 (Mitsubishi), DP-893 (Pfizer), RO-0730699 (Roche) and

combinations thereof. Non-limiting examples of such combinations include Janumet™, a combination of sitagliptin/metformin HCl (Merck).

Insulin sensitizers. Non-limiting examples of insulin sensitizers include PPAR agonists and biguanides. Non-limiting examples of PPAR agonists include glitazone and thiaglitazone agents such as rosiglitazone, rosiglitazone maleate (AVANDIA™, GlaxoSmithKline), pioglitazone, pioglitazone hydrochloride (ACTOS™, Takeda), ciglitazone and MCC-555 (Mitstubishi Chemical Co.), troglitazone and englitazone. Non-limiting example of biguanides include phenformin, metformin, metformin hydrochloride (such as GLUCOPHAGE®, Bristol-Myers Squibb), metformin hydrochloride with glyburide (such as GLUCOVANCE™, Bristol-Myers Squibb) and buformin. Other non-limiting examples of insulin sensitizers include PTP-1B inhibitors; and glucokinase activators, such as miglitol, acarbose, and voglibose.

Insulin and insulin mimetics. Non-limiting examples of orally administrable insulin and insulin containing compositions include AL-401 (AutoImmune), and the compositions disclosed in U.S. Patent Nos. 4,579,730; 4,849,405; 4,963,526; 5,642,868; 5,763,396; 5,824,638; 5,843,866; 6,153,632; 6,191,105; and International Publication No. WO 85/05029, each of which is incorporated herein by reference.

Sulfonylureas and other insulin secretagogues. Non-limiting examples of sulfonylureas and other secretagogues include glipizide, tolbutamide, glyburide, glimepiride, chlorpropamide, acetohexamide, gliamilide, gliclazide, glibenclamide, tolazamide, GLP-1, GLP-1 mimetics, exendin, GIP, secretin, nateglinide, meglitinide, glibenclamide, and repaglinide. Non-limiting examples of GLP-1 mimetics include Byetta™ (exenatide), Liraglutinide, CJC-1131 (ConjuChem), exenatide-LAR (Amylin), BIM-51077 (Ipsen/LaRoche), ZP-10 (Zealand Pharmaceuticals), and compounds disclosed in International Publication No. WO 00/07617.

Glucosidase inhibitors and alpha glucosidase inhibitors.

Glucagon receptor antagonists other than compounds of the invention.

Hepatic glucose output lowering agents other than a glucagon receptor antagonist. Non-limiting examples of hepatic glucose output lowering agents include Glucophage and Glucophage XR.

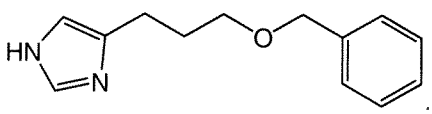
An antihypertensive agent. Non-limiting examples of antihypertensive agents include beta-blockers and calcium channel blockers (for example diltiazem, verapamil, nifedipine, amlopidine, and mybefradil), ACE inhibitors (for example captopril, lisinopril, enalapril, spirapril, ceranopril, zefenopril, fosinopril, cilazopril, and quinapril), AT-1 receptor antagonists (for example losartan, irbesartan, and valsartan), renin inhibitors and endothelin receptor antagonists (for example sitaxsentan).

A meglitinide. Non-limiting examples of meglitinides useful in the present methods for treating diabetes include repaglinide and nateglinide.

An agent that blocks or slows the breakdown of starches or sugars *in vivo*. Non-limiting examples of antidiabetic agents that slow or block the breakdown of starches and sugars *in vivo* include alpha-glucosidase inhibitors and certain peptides for increasing insulin production; Alpha-glucosidase inhibitors (which help the body to lower blood sugar by delaying the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals). Non-limiting examples of alpha-glucosidase inhibitors include acarbose; miglitol; camiglibose; certain polyamines as disclosed in WO 01/47528 (incorporated herein by reference); and voglibose.

Peptides for increasing insulin production. Non-limiting examples of suitable peptides for increasing insulin production including amlintide (CAS Reg. No. 122384-88-7, Amylin); pramlintide, exendin, certain compounds having Glucagon-like peptide-1 (GLP-1) agonistic activity as disclosed in WO 00/07617 (incorporated herein by reference).

A histamine H_3 receptor antagonist. Non-limiting examples of histamine H_3 receptor antagonist agents include the following compound:



A sodium glucose uptake transporter 2 (SGLT-2) inhibitor. Non-limiting examples of SGLT-2 inhibitors useful in the present methods include dapagliflozin and sergliflozin, AVE2268 (Sanofi-Aventis) and T-1095 (Tanabe Seiyaku).

PACAP (pituitary adenylate cyclase activating polypeptide agonists) and PACAP mimetics.

Cholesterol lowering agents. Non-limiting examples of cholesterol lowering agents include HMG-CoA reducatase inhibitors, sequestrants, nicotinyl alcohol, nicotinic acid and salts thereof, PPAR alpha agonists, PPAR alpha/gamma dual agonists, inhibitors of cholesterol absorption (such as ezetimibe (Zetia®)), combinations of HMG-CoA reductase inhibitors and cholesterol absorption agents (such as Vytorin®), acyl CoA:cholesterol acyltransferase inhibitors, anti-oxidants, LXR modulators, and CETP (cholesterolester transfer protein) inhibitors such as Torcetrapib™ (Pfizer) and Anacetrapib™ (Merck).

Agents capable of raising serum HDL cholesterol levels. Non-limiting examples include niacin (vitamin B-3), such as Niaspan™ (Kos). Niacin may be administered alone or optionally combined with one or more additional active agents such as: niacin/lovastatin (Advicor™, Abbott), niacin/simvastatin (Simcor™, Abbott), and/or niacin/aspirin.

PPAR delta agonists.

Antiobesity agents. Non-limiting examples of anti-obesity agents useful in the present methods for treating diabetes include a 5-HT2C agonist, such as lorcaserin; a neuropeptide Y antagonist; an MCR4 agonist; an MCH receptor antagonist; a protein hormone, such as leptin or adiponectin; an AMP kinase activator; and a lipase inhibitor, such as orlistat.

Ileal bile acid transporter inhibitors.

Anti-inflammatory agents, such as NSAIDs. Non-limiting examples of NSAIDS include a salicylate, such as aspirin, amoxiprin, benorilate or diflunisal; an arylalkanoic acid, such as diclofenac, etodolac, indometacin, ketorolac, nabumetone, sulindac or tolmetin; a 2-arylpropionic acid (a "profen"), such as ibuprofen, carprofen, fenoprofen, flurbiprofen, loxoprofen, naproxen, tiaprofenic acid or suprofen; a fenamic acid, such as mefenamic acid or meclofenamic acid; a pyrazolidine derivative, such as phenylbutazone, azapropazone, metamizole or oxyphenbutazone; a coxib, such as celecoxib, etoricoxib, lumiracoxib or parecoxib; an oxicam, such as piroxicam, lornoxicam, meloxicam or tenoxicam; or a sulfonanilide, such as nimesulide.

Anti-pain medications, including NSAIDs as discussed above, and opiates. Non-limiting examples of opiates include an anilidopiperidine, a phenylpiperidine, a diphenylpropylamine derivative, a benzomorphane derivative, an oripavine derivative and a morphinane derivative. Additional illustrative examples of opiates include morphine, diamorphine, heroin, buprenorphine, dipipanone, pethidine, dextromoramide, alfentanil, fentanyl, remifentanil, methadone, codeine, dihydrocodeine, tramadol, pentazocine, vicodin, oxycodone, hydrocodone, percocet, percodan, norco, dilaudid, darvocet or lorcet.

Antidepressants. Non-limiting examples of tricyclic antidepressants useful in the present methods for treating pain include amitryptyline, carbamazepine, gabapentin or pregabalin.

Protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

CB1 antagonists/inverse agonists. Non-limiting examples of CB1 receptor antagonists and inverse agonists include rimonabant and those disclosed in WO03/077847A2, published 9/25/2003, WO05/000809, published 1/6/2005, and WO2006/060461, published June 8, 2006.

In another embodiment, the present invention provides a method of treating a condition selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and an HMG-CoA reductase inhibitor.

In another embodiment, the present invention provides a method of treating a condition selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and an HMG-CoA reductase inhibitor, wherein the HMG-CoA reductase inhibitor is a statin.

In another embodiment, the present invention provides a method of treating a condition selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and

dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and an HMG-CoA reductase inhibitor, wherein the HMG-CoA reductase inhibitor is a statin selected from lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522, and rivastatin.

In another embodiment, the present invention provides a method of reducing the risk of developing, or delaying the onset of, a condition selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and an HMG-CoA reductase inhibitor.

In another embodiment, the present invention provides a method of reducing the risk of developing, or delaying the onset of, a condition selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and an HMG-CoA reductase inhibitor, wherein the HMG-CoA reductase inhibitor is a statin.

In another embodiment, the present invention provides a method of reducing the risk of developing, or delaying the onset of, a condition selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and an HMG-CoA reductase inhibitor, wherein the HMG-CoA reductase inhibitor is a statin selected from lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522, and rivastatin.

In another embodiment, the present invention provides a method of reducing the risk of developing, or delaying the onset of atherosclerosis, high LDL levels, hyperlipidemia, and dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective

amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and a cholesterol absorption inhibitor, optionally in further combination with a statin.

In another embodiment, the present invention provides a method of reducing the risk of developing, or delaying the onset of atherosclerosis, high LDL levels, hyperlipidemia, and dyslipidemia, in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount or amounts of a compound of the invention, or a composition comprising a compound of the invention, and a cholesterol absorption inhibitor, optionally in further combination with one or more statins, wherein the cholesterol absorption inhibitor is selected from ezetimibe, ezetimibe/simvastatin combination (Vytorin®), and a stanol.

In another embodiment, the present invention provides a pharmaceutical composition comprising (1) a compound according to the invention; (2) one or more compounds or agents selected from DPP-IV inhibitors, insulin sensitizers, insulin and insulin mimetics, a sulfonylurea, an insulin secretagogue, a glucosidase inhibitor, an alpha glucosidase inhibitor, a glucagon receptor antagonists other than a compound of the invention, a hepatic glucose output lowering agent other than a glucagon receptor antagonist, an antihypertensive agent, a meglitinide, an agent that blocks or slows the breakdown of starches or sugars *in vivo,* an alpha-glucosidase inhibitor, a peptide capable of increasing insulin production, a histamine H_3 receptor antagonist, a sodium glucose uptake transporter 2 (SGLT-2) inhibitor, a peptide that increases insulin production, a GIP cholesterol lowering agent, a PACAP, a PACAP mimetic, a PACAP receptor 3 agonist, a cholesterol lowering agent, a PPAR delta agonist, an antiobesity agent, an ileal bile acid transporter inhibitor, an anti-inflammatory agent, an anti-pain medication, an antidepressant, a protein tyrosine phosphatase-1B (PTP-1B) inhibitor, a CB1 antagonist, and a CB1 inverse agonist; and (3) one or more pharmaceutically acceptable carriers.

When administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in

such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts).

In one embodiment, the one or more compounds of the invention is administered during at time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

In another embodiment, the one or more compounds of the invention and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a condition.

In another embodiment, the one or more compounds of the invention and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a condition.

In still another embodiment, the one or more compounds of the invention and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a condition.

In one embodiment, the one or more compounds of the invention and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration.

The one or more compounds of the invention and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

In one embodiment, the administration of one or more compounds of the invention and the additional therapeutic agent(s) may inhibit the resistance of a condition to the agent(s).

In one embodiment, when the patient is treated for diabetes, a diabetic complication, impaired glucose tolerance or impaired fasting glucose, the other therapeutic is an antidiabetic agent which is not a compound of the invention. In another embodiment, when the patient is treated for pain, the other therapeutic agent is an analgesic agent which is not a compound of the invention.

In another embodiment, the other therapeutic agent is an agent useful for reducing any potential side effect of a compound of the invention. Non-limiting examples of such potential side effects include nausea, vomiting, headache, fever, lethargy, muscle aches, diarrhea, general pain, and pain at an injection site.

In one embodiment, the other therapeutic agent is used at its known therapeutically effective dose. In another embodiment, the other therapeutic agent is used at its normally prescribed dosage. In another embodiment, the other therapeutic agent is used at less than its normally prescribed dosage or its known therapeutically effective dose.

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of a condition described herein can be determined by the attending clinician, taking into consideration the the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the compound(s) of the invention and the other agent(s) for treating diseases or conditions listed above can be administered simultaneously or sequentially. This is particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once daily and another every six hours, or when the preferred pharmaceutical compositions are different, *e.g.* one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the one or more compounds of the invention and the additional therapeutic agent(s) can, when administered as combination therapy, range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of the therapy, the patient and the route of administration. In one embodiment, the dosage is from about 0.2 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In yet

another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In a further embodiment, the dosage is from about 1 to about 20 mg/day, administered in a single dose or in 2-4 divided doses.

As indicated above, in one embodiment, the invention provides compositions comprising an effective amount of one or more compounds of the invention or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and a pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, PA.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols

and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

In one embodiment, the compound of the invention is administered orally.

In another embodiment, the compound of the invention is administered parenterally.

In another embodiment, the compound of the invention is administered intravenously.

In one embodiment, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation is from about 0.1 to about 2000 mg. Variations will necessarily occur depending on the target of the therapy, the patient and the route of administration. In one embodiment, the unit dose dosage is from about 0.2 to about 1000 mg. In another embodiment, the unit dose dosage is from about 1 to about 500 mg. In another embodiment, the unit dose dosage is from about 1 to about 100 mg/day. In still another embodiment, the unit dose dosage is from about 1 to about 50 mg. In yet another embodiment, the unit dose dosage is from about 1 to about 10 mg.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 75 mg/day, in two to four divided doses.

When the invention comprises a combination of at least one compound of the invention and an additional therapeutic agent, the two active components

may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising at least one compound of the invention and an additional therapeutic agent in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the additional therapeutic agent can be determined from published material, and may range from about 1 to about 1000 mg per dose. In one embodiment, when used in combination, the dosage levels of the individual components are lower than the recommended individual dosages because of the advantageous effect of the combination.

Thus, the term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the various the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

In one embodiment, the components of a combination therapy regime are to be administered simultaneously, they can be administered in a single composition with a pharmaceutically acceptable carrier.

In another embodiment, when the components of a combination therapy regime are to be administered separately or sequentially, they can be administered in separate compositions, each containing a pharmaceutically acceptable carrier.

The components of the combination therapy can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc.

Kits

In one embodiment, the present invention provides a kit comprising a effective amount of one or more compounds of the invention, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, vehicle or diluent.

In another aspect the present invention provides a kit comprising an amount of one or more compounds of the invention, or a pharmaceutically acceptable salt or solvate thereof, and an amount of at least one additional therapeutic agent described above, wherein the combined amounts are effective for treating or preventing a condition described herein in a patient.

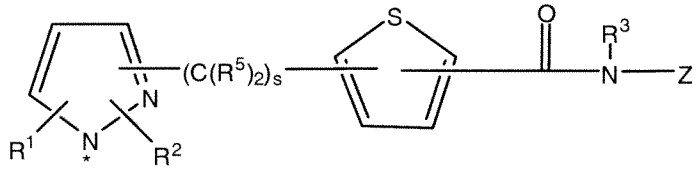
When the components of a combination therapy regime are to are to be administered in more than one composition, they can be provided in a kit comprising in a single package, one container comprising a compound of the invention in pharmaceutically acceptable carrier, and one or more separate containers, each comprising one or more additional therapeutic agents in a pharmaceutically acceptable carrier, with the active components of each composition being present in amounts such that the combination is therapeutically effective.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparant to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.

WE CLAIM:

1. A compound, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, said compound having the general structure shown in Formula (A):



(A)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

the * shown in the N* represents a valence optionally filled by R^1, R^2, or H;

s is an integer from 1 to 5;

R^1 is selected from the group consisting of:

(a) $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-C(O)NR^8R^9$, and $-NR^8R^9$;

(b) alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, $-OC(O)NR^8R^9$, unsubstituted alkoxy, and alkoxy substituted with one or more groups independently selected

from the group consisting of halo, perhaloalkoxy, OH, and $-CO_2R^6$;

(c) -O-aryl, -S-aryl, arylalkyl-, -O-heteroaryl, -S-heteroaryl, heteroarylalkyl-, cycloalkyl, aryl-fused cycloalkyl-, cycloalkylalkyl-, -O-cycloalkyl, -S-cycloalkyl, heterocycloalkyl, aryl-fused heterocycloalkyl-, heterocycloalkylalkyl-, -O-heterocycloalkyl, -S-heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, -S-cycloalkenyl, heterocycloalkenyl, -O-heterocycloalkenyl, and -S-heterocycloalkenyl,

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl portions of said -O-aryl, -S-aryl, arylalkyl-, -O-heteroaryl, -S-heteroaryl, heteroarylalkyl-, cycloalkyl, aryl-fused cycloalkyl-, cycloalkylalkyl-, -O-cycloalkyl, -S-cycloalkyl, heterocycloalkyl, aryl-fused heterocycloalkyl-, heterocycloalkylalkyl-, -O-heterocycloalkyl, -S-heterocycloalkyl, cycloalkenyl, -O-cycloalkenyl, -S-cycloalkenyl, heterocycloalkenyl, -O-heterocycloalkenyl, and -S-heterocycloalkenyl, and the alkyl portions of said arylalkyl-, said heteroarylalkyl-, said cycloalkylalkyl-, and said heterocycloalkylalkyl-, are each independently unsubstituted or optionally independently substituted with 1 or more groups each independently selected from the group consisting of:

(i) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^8-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(ii) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl,

and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(iii) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (i) and (ii) above;

and

(d) aryl and heteroaryl,

wherein said aryl and said heteroaryl are substituted with at least one group each independently selected from the group consisting of:

(1) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SF_5$, $-Si(R^7)_3$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(2) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl,

-heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(3) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (1) and (2) above;

R^2 is selected from the group consisting of aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein the aryl and heteroaryl, and the aryl and heteroaryl portions of said arylalkyl- and said heteroarylalkyl-, are substituted with 1 or more groups each independently selected from the group consisting of:

(A) halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SF_5$, $-Si(R^7)_3$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$,

(B) -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl, -O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and -O-heteroalkynyl,

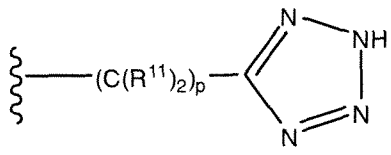
wherein each of the alkyl, alkenyl and alkynyl portions of said -alkyl, -heteroalkyl, -C(O)alkyl, -C(O)-heteroalkyl, -O-alkyl,

-O-heteroalkyl, -alkenyl, -heteroalkenyl, -C(O)alkenyl, -C(O)-heteroalkenyl, -O-alkenyl, -O-heteroalkenyl, -alkynyl, -heteroalkynyl, -C(O)alkynyl, -C(O)-heteroalkynyl, -O-alkynyl, and –O-heteroalkynyl are unsubstituted or optionally independently substituted with one or more groups each independently selected from the group consisting of:

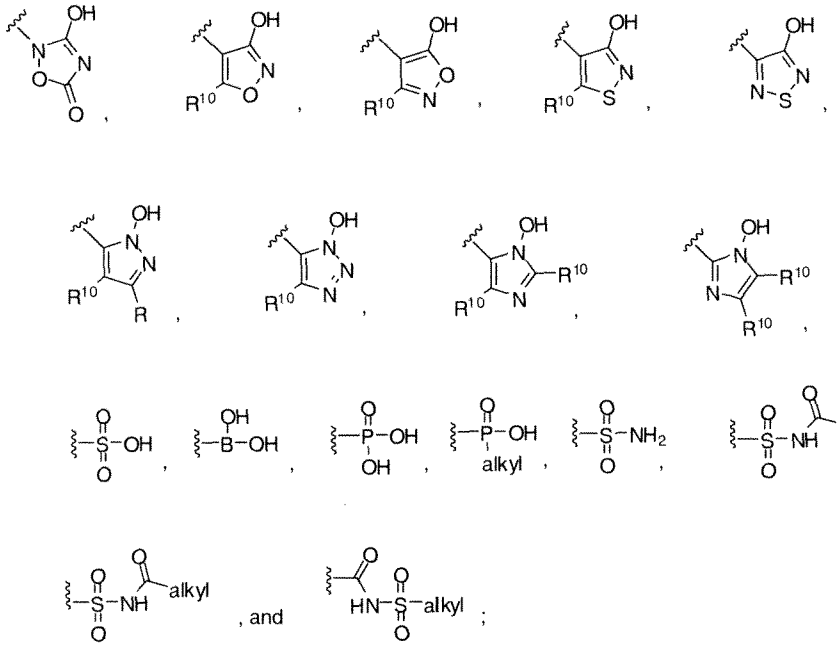
halo, OH, $-CO_2R^6$, $-C(O)R^6$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, CN, NO_2, $-C(O)NR^8R^9$, $-NR^8R^9$, haloalkoxy, $-NR^{10}-C(O)-NR^8R^9$, $-NR^{10}-CO_2R^6$, $-NR^{10}-C(O)R^6$, $-NR^{10}-SO_2R^6$, $-SO_2-NR^8R^9$, $-C(O)NR^8R^9$, and $-OC(O)NR^8R^9$, and

(C) aryl, -O-aryl, -C(O)-aryl, heteroaryl, -O-heteroaryl, -C(O)-heteroaryl, cycloalkyl, -O- cycloalkyl, -C(O)- cycloalkyl, heterocycloalkyl, -O- heterocycloalkyl, -C(O)- heterocycloalkyl, cycloalkenyl, -O- cycloalkenyl, -C(O)- cycloalkenyl, and heterocycloalkenyl, -O- heterocycloalkenyl, -C(O)-heterocycloalkenyl, each of which is unsubstituted or optionally independently substituted with from 1 to 2 groups each independently selected from (A) and (B) above;

R^3 is selected from the group consisting of H and lower alkyl;

Z is a moiety selected from $-(C(R^{11})_2)-(C(R^{12}R^{13}))_m-C(O)OH$, $-(C(R^{11})_2)-(C(R^{14})_2)_n-C(O)OH$, from $-(C(R^{11})_2)-(C(R^{12}R^{13}))_m-C(O)Oalkyl$, $-(C(R^{11})_2)-(C(R^{14})_2)_n-C(O)Oalkyl$,  , $-(C(R^{11})_2)-(C(R^{12}R^{13}))_m-Q$, and $-(C(R^{11})_2)-(C(R^{14})_2)_n-Q$,

wherein Q is a moiety selected from the group consisting of:



m is an integer from 0 to 5;

n is an integer from 0 to 5;

p is an integer from 0 to 5;

each R^5 is independently selected from the group consisting of H, lower alkyl, hydroxy-substituted lower alkyl;

each R^6 is independently selected from the group consisting of H and alkyl;

each R^7 is independently selected from the group consisting of H, alkyl, aryl, arylalkyl-;

each R^8 is independently selected from the group consisting of H and alkyl;

each R^9 is independently selected from the group consisting of H and alkyl,

or alternatively R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-, 6-, or 7-membered saturated heterocyclic ring, or a 5-, 6-, or 7-membered unsaturated heterocyclic ring, which ring contains (including said nitrogen) from 1 to 2 ring heteroatoms each independently selected from the group consisting of N, N-oxide, O, S, S(O), or $S(O)_2$,

or alternatively R^8 and R^9 are taken together with the nitrogen to which they are attached to form a 5-membered heteroaromatic ring containing (including the nitrogen to which R^8 and R^9 are attached) from 1 to 3 ring nitrogens;

each R^{10} is independently selected from the group consisting of H and alkyl;

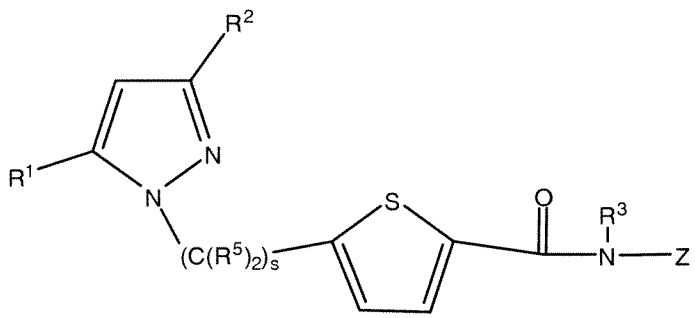
each R^{11} is independently selected from the group consisting of H and lower alkyl;

each R^{12} is independently selected from the group consisting of H, lower alkyl, -OH, hydroxy-substituted lower alkyl;

each R^{13} is independently selected from the group consisting of H, unsubstituted lower alkyl, lower alkyl substituted with one or more groups each independently selected from the group consisting of hydroxyl and alkoxy, or R^{12} and R^{13} are taken together to form an oxo; and

each R^{14} is independently selected from the group consisting of H and fluoro.

2. A compound, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, said compound having the general structure shown in Formula (VI):



(VI)

wherein R^1, R^2, R^3, R^5, s, and Z are selected independently of each other and wherein:

R^1 is selected from the group consisting of:

phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 3 groups each independently selected from: halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl;

R^2 is selected from the group consisting of:

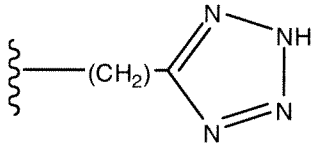
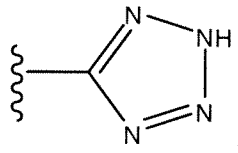
phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 3 groups each independently selected from: halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl;

R^3 is selected from the group consisting of H and lower alkyl;

R^5 is selected from H and alkyl;

s is 1-3; and

Z is selected from the group consisting of $-(CH_2)-(CH(CH_3))-C(O)OH$, $-(CH_2)-(CH_2)-(CH_2)-C(O)OH$, $-(CH_2)-C(CH_3)_2-C(O)OH$, $-(CH_2)-C(CH_3)(OH)-C(O)OH$, $-CH_2-CH_2-C(O)OH$, $-CH_2-CH(OH)-C(O)OH$, $-CH(CH_3)-CH_2-C(O)OH$, $-CH_2-CH(F)-C(O)OH$, $-CH_2-CF_2-C(O)OH$, $-CH(CH_3)-CF_2-C(O)OH$, $-CH_2-CH_2-CF_2-C(O)OH$,  , and  .

3. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

R^1 is selected from phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 2 groups each independently selected from: halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is selected from the group consisting of:

phenyl and naphthyl,

wherein said phenyl and said naphthyl are substituted with from 1 to 2 groups each independently selected from: halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

4. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

one of R^1 and R^2 is phenyl and the other is naphthyl,

wherein each of said phenyl and said naphthyl is substituted with from 1 to 2 groups each independently selected from: halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

5. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

R^1 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:
halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is naphthyl,

wherein said naphthyl is substituted with from 1 to 2 groups each independently selected from:
halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

6. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

R^1 is naphthyl,

wherein said naphthyl is substituted with from 1 to 2 groups each independently selected from:
halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:
halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

7. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

R^1 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl; and

R^2 is phenyl,

wherein said phenyl is substituted with from 1 to 2 groups each independently selected from:

halo, alkyl, haloalkyl, alkoxy, haloalkoxy, and cycloalkyl.

8. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

R^3 is selected from the group consisting of H and methyl.

9. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

Z is selected from the group consisting of $-(CH_2)-(CH(CH_3))-C(O)OH$, $-(CH_2)-(CH_2)-(CH_2)-C(O)OH$, $-(CH_2)-C(CH_3)_2-C(O)OH$, $-(CH_2)-C(CH_3)(OH)-C(O)OH$, $-CH_2-CH_2-C(O)OH$, $-CH_2-CH(OH)-C(O)OH$, $-CH(CH_3)-CH_2-C(O)OH$, $-CH_2-CH(F)-C(O)OH$, $-CH_2-CF_2-C(O)OH$, $-CH(CH_3)-CF_2-C(O)OH$, and $-CH_2-CH_2-CF_2-C(O)OH$.

10. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

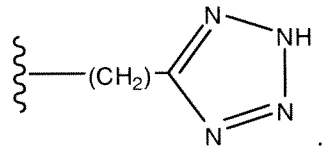
R^3 is H; and

Z is selected from the group consisting of $-(CH_2)-(CH(CH_3))-C(O)OH$, $-(CH_2)-(CH_2)-(CH_2)-C(O)OH$, $-(CH_2)-C(CH_3)_2-C(O)OH$, $-(CH_2)-C(CH_3)(OH)-C(O)OH$, $-CH_2-CH_2-C(O)OH$, $-CH_2-CH(OH)-C(O)OH$, -

$CH(CH_3)$-CH_2-C(O)OH, -CH_2-CH(F)-C(O)OH, -CH_2-CF_2-C(O)OH, -$CH(CH_3)$-CF_2-C(O)OH, and -CH_2-CH_2-CF_2-C(O)OH.

11. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

R^3 is H; and

Z is 

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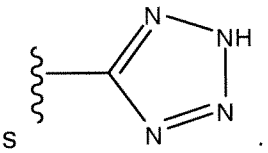
12. A compound of claim 2, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, wherein:

R^3 is H; and

Z is 

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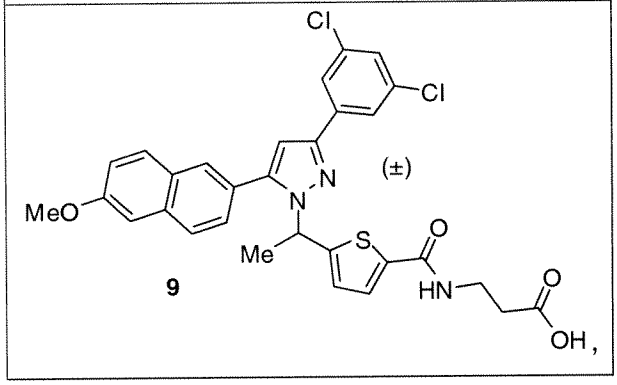
13. A compound, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, selected from the group consisting of:

Compound

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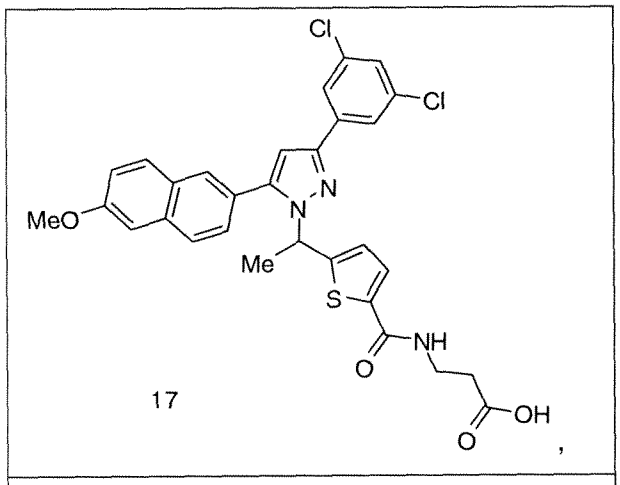

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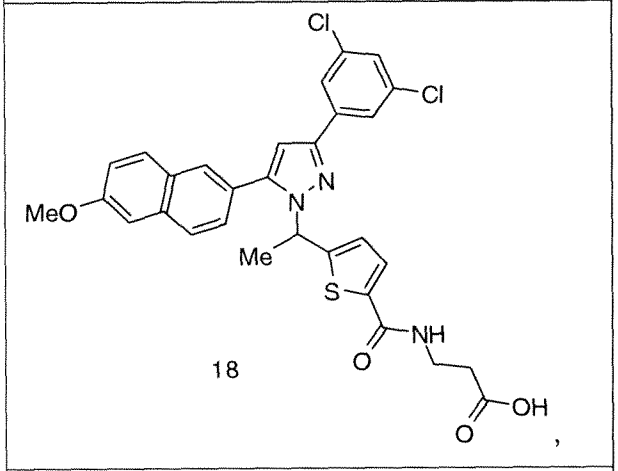

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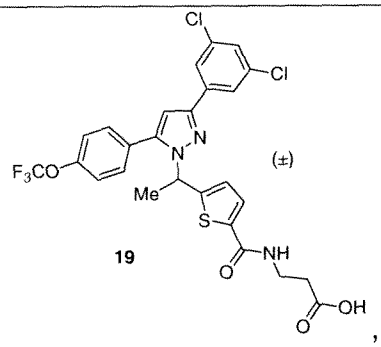

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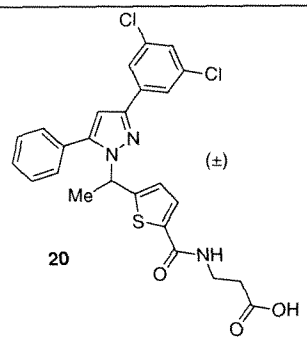
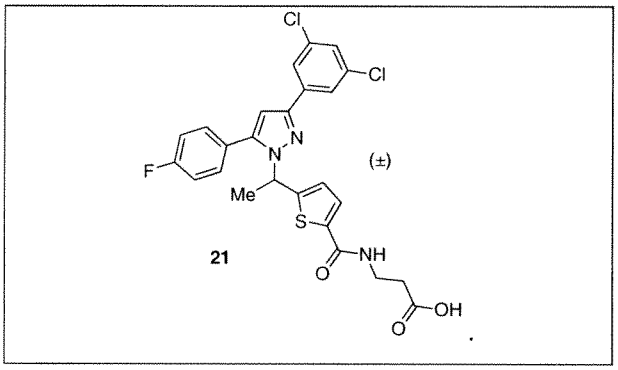


20 , and



14. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of said compound, tautomer, or isomer, and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition according to claim 14, further comprising a at least one antidiabetic agent other than a compound of claim 1.

16. A pharmaceutical composition according to claim 15, wherein said at least one antidiabetic agent other than a compound of claim 1 is selected from: a DPP-IV inhibitor, an insulin sensitizer, insulin, an insulin mimetic, an insulin secretagogue, a glucosidase inhibitor, an alpha glucosidase inhibitor, a glucagon receptor antagonist other than a compound of claim 1, glucophage, glucophage XR, an antihypertensive agent, a meglitinide, an alpha-glucosidase inhibitor, amlintide, pramlintide, exendin, a histamine H_3 receptor antagonist, dapagliflozin, sergliflozin, AVE2268 (Sanofi-Aventis) and T-1095 (Tanabe Seiyaku), a cholesterol lowering agent, a PACAP, a PACAP mimetic, a PACAP receptor 3 agonist, a PPAR delta agonist, an antiobesity agent, an ileal bile acid transporter inhibitor, an NSAID, and a CB1 receptor antagonist, and a CB1 receptor inverse agonist.

17. A method for treating or delaying the onset of type 2 diabetes mellitus in a patient in need thereof comprising administering to said patient a compound of any one of claims 1-13 in an amount that is effective to treat type 2 diabetes mellitus.

18. A method for treating a condition, or a combination of conditions, selected from hyperglycemia, low glucose tolerance, insulin resistance, obesity, abdominal obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and/or high LDL levels, atherosclerosis, atherosclerosis and its sequelae, vascular restenosis, pancreatitis, neurodegenerative disease, retinopathy, nephropathy, neuropathy, Syndrome X and other conditions where insulin resistance or hyperglycemia is a component, in a patient in need thereof, comprising administering to said patient a compound of any one of claims 1-13 in an amount effective to treat said condition.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/038113

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/06 A61K31/4155 A61P3/10
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 348 480 B1 (KUBOTA HIROKAZU [JP] ET AL) 19 February 2002 (2002-02-19) table 3	1-18
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A	US 2005/272794 A1 (PARMEE EMMA R [US] ET AL) 8 December 2005 (2005-12-08) the whole document	1-18

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2010	06/09/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/038113

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 2009/035558 A1 (MERCK & CO INC [US]; COHEN BENJAMIN M [US]; KUMKE DANIEL J [US]; TAN L) 19 March 2009 (2009-03-19) the whole document	1-18
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Information on patent family members

International application No
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