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(54) Title: HETEROCYCLIC MODULATORS OF TGR5

(57) Abstract: The present invention relates to heterocyclic compounds useful as modulators of TGR5 and methods for the treatment of prevention of metabolic, cardiovascular, and inflammatory diseases.

HETEROCYCLIC MODULATORS OF TGR5

[001] This application claims the benefit of priority of United States provisional application No. 60/867,583, filed November 28, 2006, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[002] Disclosed herein are new heterocyclic compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods of modulation of TGR5 activity in a human or animal subject are also provided for the treatment diseases such as metabolic, cardiovascular, and inflammatory diseases, for example diabetes, obesity, myocardial infarction, angina pectoris, coronary artery disease, atherosclerosis, cardiac hypertrophy, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), psoriasis, ulcerative colitis, allergic diseases, fatty liver, liver fibrosis, kidney fibrosis, anorexia nervosa and bulimia nervosa.

[003] Obesity is a growing threat to the global health by virtue of its association with a cluster of diseases that include insulin resistance, glucose intolerance, dyslipidemia, and hypertension, collectively known as the metabolic syndrome or syndrome X. It is well documented that patients with metabolic syndrome have a higher risk for coronary heart disease and stroke [Grundy S. M. et al. Circulation 112:e285-e290, 2005]. The treatment of obesity will require complex solutions, including increased public awareness to diminish food portions, improved food choices and increased physical activity. However, epidemiologic studies have shown that treating diabetes/insulin resistance in these patients can reduce the risk of coronary artery disease. Marketed drugs to treat diabetes and insulin resistance include biguanides (such as metformin), peroxisome proliferator activated receptor gamma (PPARγ) agonists (such as rosiglitazone and pioglitazone), sulphonylureas, and most recently GLP-1 mimetics such as Exenatide (Byetta). However, there remains a need for additional agents that can perhaps treat the root cause(s) of metabolic syndrome by treating obesity and diabetes. TGR5 modulators described herein might represent such an opportunity.

[004] Bile acids (BA) are amphipathic molecules which are synthesized in the liver from cholesterol and stored in the gall bladder until secretion to the duodenum and intestine to play an important role in the solubilization and absorption of dietary fat and lipid-soluble vitamins. Approx. 99% of BA are absorbed again by passive diffusion and active transport in the terminal ileum and transported back to the liver via the portal vein (enterohepatic circulation). In the liver, BA decrease their own biosynthesis from cholesterol through the activation of the farnesoid X receptor alpha (FXRα) and small heterodimer partner (SHP), leading to the transcriptional repression of cholesterol 7α-hydroxylase, the rate-limiting step of BA biosynthesis from cholesterol.

[005] Recently, two groups independently discovered the GPCR, TGR5 (aka M-BAR) which responds to bile acids [Kawamata Y. et al, J. Biol. Chem., 278:9435-9440, 2003; Maruyama T. et al. Biochem. Biophs. Res. Commun. 298 , 714-719, 2002]. TGR5 is a seven transmembrane Gs-coupled GPCR and stimulation by ligand binding causes activation of adenylyl cyclase which leads to the elevation of intracellular cAMP and subsequent activation of downstream signaling pathways. The human receptor shares 86, 90, 82, and 83% amino acid identity to bovine, rabbit, rat, and mouse receptor, respectively. TGR5 is abundantly expressed in the lung, spleen, small intestine, placenta and mononuclear cells (Kawamata Y. et al, J. Biol. Chem., 278:9435-9440, 2003). Bile acids induced receptor internalization, intracellular cAMP production and activation of exrtacellular signal-regulated kinase in TGR5-expressing HEK293 and CHO cells. In addition, TGR5 was found to be abundantly expressed in monocytes/macrophages from humans and rabbits (Kawamata Y. et al, J. Biol. Chem., 278:9435-9440, 2003), and bile acid treatment suppressed LPS-induced cytokine production in rabbit alveolar macrophages and human THP-1cells expressing TGR5. These data suggest that bile acids can suppress the macrophage function via activation of TGR5.

[006] Maruyama et al. [Maruyama T. et al. Biochem. Biophs. Res. Commun. 298 , 714-719, 2002] showed that TGR5 is expressed in intestinal enteroendocrine cell lines from human (NCI-H716) and murine (STC-1, GLUTag) origin, but not in the intestinal epithelial cells (CaCo-2 and HT-29). Stimulation of TGR5 by BA in NCI-H716 cells

stimulated cAMP production. This suggested that bile acids may induce the secretion of glucagon-like peptide-1 (GLP-1) or cholecystokinin (CCK) from the enteroendocrine cells through TGR5 stimulation, since cAMP stimulated the secretion of GLP-1 and CCK from these cells [Reimer R.A. et al. Endocrinology 142, 4522-4528, 2001; Chang C.H. et al. Am. J. Physiol. 271, G516-G523, 1996; Brubaker P.L. et al, Endocrinology 139, 4108-4114, 1998]. This hypothesis was recently confirmed in a publication by Katsuma S. et al. who demonstrated that activation of TGR5 by BA promoted GLP-1 in STC-1 cells [Katsuma S. et al. Biochem. Biophys. Res. Commun. 329, 386-390, 2005]. RNA interference experiments revealed that reduced expression of TGR5 resulted in reduced secretion of GLP-1. GLP-1 has been shown to stimulate insulin release in a glucose dependent manner in humans [Kreymann et al. Lancet 2 (8571) 1300-1304, 1987] and studies in experimental animals demonstrated that this incretin hormone is necessary for normal glucose homeostasis. In addition, GLP-1 can exert several beneficial effects in diabetes and obesity, including 1) increased glucose disposal, 2) suppression in glucose production, 3) reduced gastric emptying, 4) reduction in food intake and 5) weight loss.

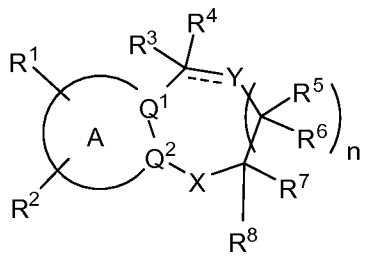
[007] Furthermore, recently published data suggested that activation of TGR5 might be beneficial for the treatment of obesity and diabetes. Watanabe et al. (Nature, 439, 484-489, 2006) reported that mice fed high fat diet (HFD) containing 0.5% cholic acid gained less weight than control mice on HFD alone. There was no difference between the two groups in terms of food intake. These effects were independent of FXR-alpha, and instead stem from the binding of bile acids to TGR5 and the subsequent induction of the cAMP-dependent thyroid hormone activating enzyme type 2 (D2) which converts the inactive T3 into the active T4 , leading to stimulation of the thyroid hormone receptor and promoting energy expenditure. Mice lacking the D2 gene ($D2^{-/-}$) were resistant to cholic acid-induced weight loss. In both rodents and humans, the most thermogenically important tissues (the brown adipose and skeletal muscle) are specifically targeted by this mechanism because they co-express D2 and TGR5. The BA-TGR5-cAMP-D2 signaling pathway is therefore a crucial mechanism for fine-tuning energy homeostasis that can be targeted to improve metabolic control.

[008] Taken together, a small molecule TGR5 modulator could be used for the treatment of obesity, diabetes and a wide range of acute and chronic inflammatory diseases.

[009] Recently, certain substituted heterocyclic compounds have been described as agonists of TGR5 for the treatment of metabolic, cardiovascular, and inflammatory diseases (EP01/591120A1, WO04/043468A1, WO04/067008A1, and JP24346059A2). However, as none of these compounds have yet been approved for use in the treatment of disease, a need still exists in the art to provide novel modulators of TGR5.

[010] Novel compounds and pharmaceutical compositions, certain of which have been found to modulate TGR5 have been discovered, together with methods of synthesizing and using the compounds including methods for the treatment of TGR5-mediated diseases in a patient by administering the compounds.

[011] In certain embodiments of the present invention, compounds have structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano,

cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

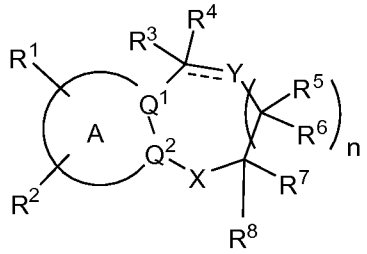
R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[012] Certain compounds disclosed herein may possess useful TGR5 modulating activity, and may be used in the treatment or prophylaxis of a disease or condition in which TGR5 plays an active role. Thus, in broad aspect, certain embodiments also provide pharmaceutical compositions comprising one or more compounds disclosed

herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. Certain embodiments provide methods for modulating TGR5. Other embodiments provide methods for treating a TGR5-mediated disorder in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. Also provided is the use of certain compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the modulation of TGR5.

[013] In certain embodiments, a method of treatment of a TGR5-mediated disease comprises the administration, to a patient in need thereof, of a therapeutically effective amount of a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

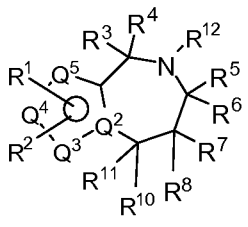
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[014] In further embodiments, said compound has structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

Q^2 is selected from the group consisting of N and C;

Q^3, Q^4, and Q^5 are independently selected from the group consisting of N and C, any of which may be optionally substituted by a substituent selected from the group consisting of hydrogen, R^1, and R^2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

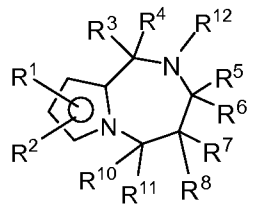
R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[015] In yet further embodiments said compound has structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be

optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

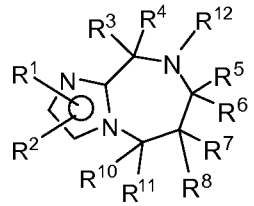
[016] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[017] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group

consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[018] In yet further embodiments R^3 is 2-methylphenyl.

[019] In further embodiments said compound has structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

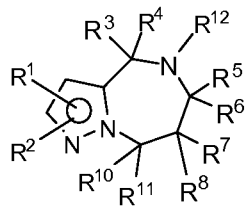
[020] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally

substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[021] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[022] In yet further embodiments R^3 is 2-methylphenyl.

[023] In further embodiments said compound has structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[024] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[025] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[026] In yet further embodiments R^3 is 2-methylphenyl.

[027] In yet further embodiments said compound is selected from the group consisting of Examples 1 to 13.

[028] In yet further embodiments said disease is a metabolic disease.

[029] In yet further embodiments said disease is selected from the group consisting of inadequate glucose tolerance, insulin resistance, type I diabetes, and type II diabetes.

[030] In yet further embodiments the method further comprises the administration of another therapeutic agent.

[031] In yet further embodiments said agent is selected from the group consisting of insulin, metformin, Glipizide, glyburide, Amaryl, gliclazide, meglitinides, nateglinide, repaglinide, pramlintide, PTP-112, SB-517955, SB-4195052, SB-216763, NN-57-05441, NN-57-05445, GW-0791, AGN-$^{19}4^{20}4$, T-1095, BAY R3401, acarbose, miglitol, voglibose, Exendin-4, DPP728, LAF237, vildagliptin , BMS477118, PT-100, GSK-823093, PSN-9301, T-6666, SYR-322, SYR-619, Liraglutide, CJC-1134-PC, naliglutide, MK-0431, saxagliptin, GSK23A, pioglitazone, rosiglitazone, AVE2268, GW869682, GSK189075, APD668, PSN-119-1, PSN-821, rosuvastatin, atrovastatin, simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, fenofibrate, benzafibrate, clofibrate, gemfibrozil, Ezetimibe, eflucimibe, CP-529414, CETi-1, JTT-705, cholestyramine, colestipol, niacin, implitapide, (*R*)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}2,3-dihydro-l*H*-indole-2-carboxylic acid, and GI-262570.

[032] In yet further embodiments said disease is associated with perturbed bile acid metabolism.

[033] In yet further embodiments the method further comprises the administration of another therapeutic agent.

[034] In yet further embodiments said disease is an inflammatory disease.

[035] In yet further embodiments said disease is selected from the group consisting of rheumatoid arthritis, ulcerative colitis, and inflammatory bowel disease.

[036] In yet further embodiments the method further comprises the administration of another therapeutic agent.

[037] In yet further embodiments said agent is selected from the group consisting of betamethasone dipropionate, betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream, guaifenesin, amitryptiline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin, clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil, acetaminophen, infliximab, etanerecept, infliximab, and capsaicin.

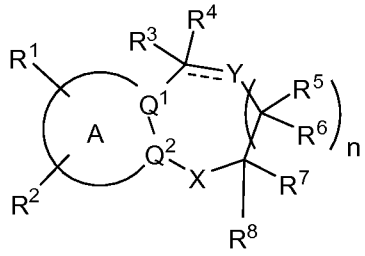
[038] In yet further embodiments said disease is obesity.

[039] In yet further embodiments said method has achieves an effect selected from the group consisting of decreasing body weight and controlling weight gain.

[040] In yet further embodiments the methodfurther comprises the administration of another therapeutic agent.

[041] In yet further embodiments said agent is selected from the group consisting of sibutramine, bromocriptine, Orlistat, rimonabant, Axokine, and bupropion.

[042] In further embodiments a method for achieving an effect selected from the group consisting of improving glucose tolerance, decreasing insulin resistance, decreasing body weight, controlling weight gain, modulation of type I diabetes, modulation of type II diabetes, modulation of perturbed bile acid metabolism, modulation of rheumatoid arthritis, modulation of ulcerative colitis, and modulation of inflammatory bowel disease in a patient comprises the administration of a therapeutically effective amount of a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

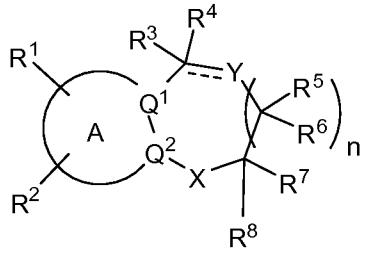
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[043] In further embodiments a method of modulation of TGR5 comprises contacting TGR5 with a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be

optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

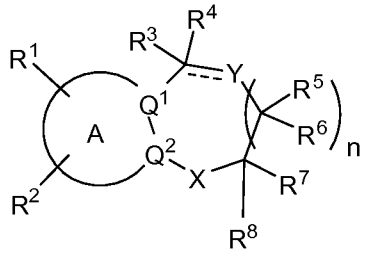
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[044] In further embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier together with a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

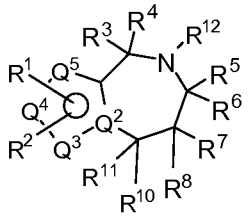
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[045] In yet further embodiments said compound has structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

Q^2 is selected from the group consisting of N and C;

Q^3, Q^4, and Q^5 are independently selected from the group consisting of N and C, any of which may be optionally substituted by a substituent selected from the group consisting of hydrogen, R^1, and R^2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

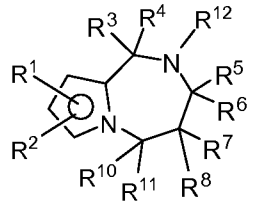
R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[046] In yet further embodiments said compound has structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

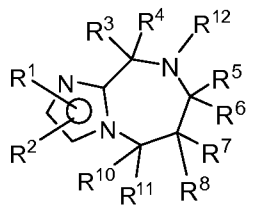
R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[047] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[048] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[049] In yet further embodiments R^3 is 2-methylphenyl.

[050] In yet further embodiments said compound has structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

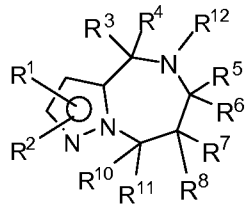
R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[051] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[052] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[053] In yet further embodiments R^3 is 2-methylphenyl.

[054] In yet further embodiments said compound has structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

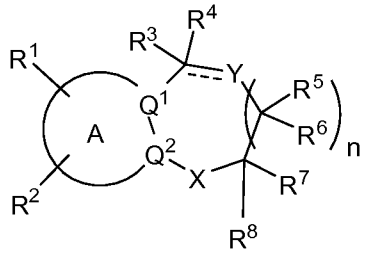
[055] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[056] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[057] In yet further embodiments R^3 is 2-methylphenyl.

[058] In further embodiments a pharmaceutical composition comprises a pharmaceutically acceptable carrier together with a compound selected from the group consisting of Examples 1 to 13.

[059] In further embodiments a compound has structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

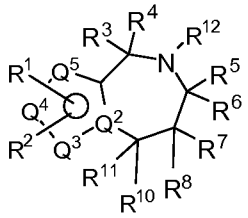
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[060] In yet further embodiments said compound has structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

Q^2 is selected from the group consisting of N and C;

Q^3, Q^4, and Q^5 are independently selected from the group consisting of N and C, any of which may be optionally substituted by a substituent selected from the group consisting of hydrogen, R^1, and R^2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

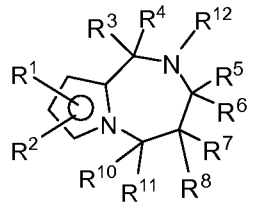
R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[061] In yet further embodiments said compound has structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

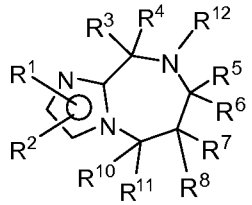
R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[062] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is

selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[063] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[064] In yet further embodiments said compound has structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

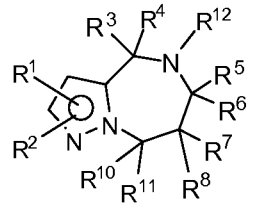
R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[065] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[066] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[067] In yet further embodiments said compound has structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

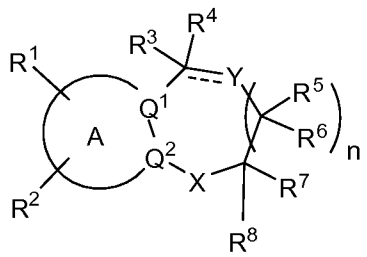
R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

[068] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[069] In yet further embodiments R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; and R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

[070] In further embodiments a compound is selected from the group consisting of Examples 1 to 13.

[071] In further embodiments a compound for use as a medicament has structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

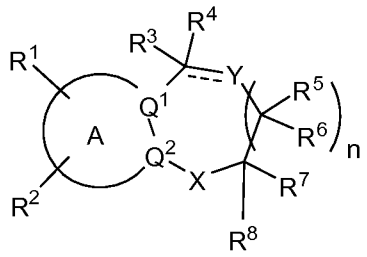
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[072] In further embodiments a compound for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the modulation of TGR5 has structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

[073] As used herein, the terms below have the meanings indicated.

[074] When ranges of values are disclosed, and the notation "from n_1 … to n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM, 3 μM, and everything in between to any number of significant figures (e.g., 1.255 μM, 2.1 μM, 2.9999 μM, etc.).

[075] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be

included by rounding up or down to that figure as well, taking into account significant figures.

[076] The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[077] The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

[078] The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[079] The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($–CH_2–$). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[080] The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[081] The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

[082] The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[083] The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. The term "alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term "alkynyl" may include "alkynylene" groups.

[084] The terms "amido" and "carbamoyl,"as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term "C-amido" as used herein, alone or in combination, refers to a -C(=O)-NR_2 group with R as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(=O)NH- group, with R as defined herein. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($CH_3C(O)NH$–).

[085] The term “amino,” as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[086] The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[087] The term “arylalkenyl” or “aralkenyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[088] The term “arylalkoxy” or “aralkoxy,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[089] The term “arylalkyl” or “aralkyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[090] The term “arylalkynyl” or “aralkynyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

[091] The term “arylalkanoyl” or “aralkanoyl” or “aroyl,”as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, napthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

[092] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[093] The terms “benzo” and “benz,” as used herein, alone or in combination, refer to the divalent radical C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

[094] The term "carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid (–NHCOO–) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

[095] The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR', group-with R and R' as defined herein.

[096] The term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group, with R and R' as defined herein.

[097] The term "carbonyl," as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

[098] The term "carboxyl" or "carboxy," as used herein, refers to –C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O– group, where R is as defined herein. A "C-carboxy" group refers to a –C(O)OR groups where R is as defined herein.

[099] The term "cyano," as used herein, alone or in combination, refers to –CN.

[0100] The term "cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronapthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[0101] The term "ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[0102] The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[0103] The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[0104] The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0105] The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($–CF_2–$), chloromethylene (–CHCl–) and the like.

[0106] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

[0107] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 7 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom selected from the group consisting of O, S, and N. In certain

embodiments, said heteroaryl will comprise from 5 to 7 carbon atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0108] The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur In certain embodiments, said hetercycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said hetercycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said hetercycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said hetercycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said hetercycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl,

dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihy-dropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

[0109] The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., –N–N–.

[0110] The term "hydroxy," as used herein, alone or in combination, refers to –OH.

[0111] The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[0112] The term "imino," as used herein, alone or in combination, refers to =N–.

[0113] The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N–O–.

[0114] The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of any one of the formulas disclosed herein.

[0115] The term "isocyanato" refers to a –NCO group.

[0116] The term "isothiocyanato" refers to a –NCS group.

[0117] The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

[0118] The term "lower," as used herein, alone or in a combination, where not otherwise specifically defined, means containing from 1 to and including 6 carbon atoms.

[0119] The term "lower aryl," as used herein, alone or in combination, means phenyl or naphthyl, which may be optionally substituted as provided.

[0120] The term "lower heteroaryl," as used herein, alone or in combination, means either 1) monocyclic heteroaryl comprising five or six ring members, of which between one and four said members may be heteroatoms selected from the group consisting of O, S, and N, or 2) bicyclic heteroaryl, wherein each of the fused rings comprises five or six ring members, comprising between them one to four heteroatoms selected from the group consisting of O, S, and N.

[0121] The term "lower cycloalkyl," as used herein, alone or in combination, means a monocyclic cycloalkyl having between three and six ring members. Lower cycloalkyls may be unsaturated. Examples of lower cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0122] The term "lower heterocycloalkyl," as used herein, alone or in combination, means a monocyclic heterocycloalkyl having between three and six ring members, of which between one and four may be heteroatoms selected from the group consisting of O, S, and N. Examples of lower heterocycloalkyls include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholinyl. Lower heterocycloalkyls may be unsaturated.

[0123] The term "lower amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, lower alkyl, and lower heteroalkyl, any of which may be optionally substituted. Additionally, the R and R' of a lower amino group may combine to form a five- or six-membered heterocycloalkyl, either of which may be optionally substituted.

[0124] The term "mercaptyl" as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.

[0125] The term "nitro," as used herein, alone or in combination, refers to $–NO_2$.

[0126] The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

[0127] The term "oxo," as used herein, alone or in combination, refers to =O.

[0128] The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[0129] The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0130] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[0131] The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

[0132] The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

[0133] The term "sulfonyl," as used herein, alone or in combination, refers to –$S(O)_2$–.

[0134] The term "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

[0135] The term "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

[0136] The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

[0137] The term "thiol," as used herein, alone or in combination, refers to an –SH group.

[0138] The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[0139] The term "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R'as defined herein.

[0140] The term "O-thiocarbamyl" refers to a –OC(S)NRR', group with R and R'as defined herein.

[0141] The term "thiocyanato" refers to a –CNS group.

[0142] The term "trihalomethanesulfonamido" refers to a $X_3CS(O)_2NR$– group with X is a halogen and R as defined herein.

[0143] The term "trihalomethanesulfonyl" refers to a $X_3CS(O)_2$– group where X is a halogen.

[0144] The term "trihalomethoxy" refers to a X_3CO– group where X is a halogen.

[0145] The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethysilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

[0146] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite

group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[0147] When a group is defined to be "null," what is meant is that said group is absent.

[0148] The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

[0149] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group

consisting of hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as –C(O)N(R)– may be attached to the parent moiety at either the carbon or the nitrogen.

[0150] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms,as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable

solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0151] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0152] The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0153] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0154] "TGR5 modulator" is used herein to refer to a compound that exhibits an EC_{50} with respect to TGR5 activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the cAMP production assay and glucagon-like peptide-1 (GLP-1) secretion assays described generally hereinbelow. "EC_{50}" is that concentration of modulator which either activates or reduces the activity of an enzyme (e.g., (TGR5)) to half-maximal level. Certain compounds disclosed herein have been discovered to exhibit modulatory activity against TGR5. In certain embodiments, compounds will exhibit an EC_{50} with respect to TGR5 of no more than about 10 μM; in further embodiments, compounds will exhibit an EC_{50} with respect to

TGR5 of no more than about 5 μM; in yet further embodiments, compounds will exhibit an EC_{50} with respect to TGR5 of not more than about 1 μM; in yet further embodiments, compounds will exhibit an EC_{50} with respect to TGR5 of not more than about 200 nM, as measured in the TGR5 assay described herein.

[0155] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

[0156] The term “therapeutically acceptable” refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0157] As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term “patient” means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

[0158] The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage

or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0159] The compounds disclosed herein can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

[0160] The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl

chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0161] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0162] While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions

disclosed herein may be manufactured in any manner known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0163] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0164] Formulations of the compounds disclosed herein suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0165] Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound

moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0166] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0167] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable

lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0168] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0169] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[0170] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[0171] Certain compounds disclosed herein may be administered topically, that is by non-systemic administration. This includes the application of a compound disclosed herein externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[0172] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation.

In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

[0173] For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0174] Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

[0175] It should be understood that in addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0176] Compounds may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

[0177] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[0178] The compounds can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

[0179] In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[0180] Specific, non-limiting examples of possible combination therapies include use of certain compounds of the invention with agents found in the following pharmacotherapeutic classifications as indicated below. These lists should not be construed to be closed, but should instead serve as illustrative examples common to the

relevant therapeutic area at present. Moreover, combination regimens may include a variety of routes of administration and should include oral, intravenous, intraocular, subcutaneous, dermal, and inhaled topical.

[0181] For the treatment of metabolic disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: insulin, insulin derivatives and mimetics, insulin secretagogues, insulin sensitizers, biguanide agents, alpha-glucosidase inhibitors, insulinotropic sulfonylurea receptor ligands, meglitinides, protein tyrosine phosphatase-lB (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors , GLP-1 (glucagon like peptide-1), GLP-1 analogs, DPPIV (dipeptidyl peptidase IV) inhibitors, RXR ligands, sodium-dependent glucose co-transporter (SGLT2) inhibitors, glycogen phosphorylase A inhibitors, an AGE breaker, PPAR modulators, non-glitazone type PPARδ agonist, HMG-CoA reductase inhibitors, cholesterol-lowering drugs and anti-obesity agents.

[0182] For the treatment of metabolic disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: insulin, metformin, Glipizide, glyburide, Amaryl, gliclazide, meglitinides, nateglinide, repaglinide, amylin mimetics (for example, pramlintide), PTP-112, SB-517955, SB-4195052, SB-216763, NN-57-05441, NN-57-05445, GW-0791, AGN-$^{19}4^{20}4$, T-1095, BAY R3401, acarbose, miglitol, voglibose, Exendin-4, DPP728, LAF237, vildagliptin , BMS477118, PT-100, GSK-823093, PSN-9301, T-6666, SYR-322, SYR-619, Liraglutide, CJC-1134-PC, naliglutide, MK-0431, saxagliptin, GSK23A, pioglitazone, rosiglitazone, AVE2268, GW869682, GSK189075, GPR119 agonists including, but not limited to APD668, PSN-119-1 and PSN-821, HMG-CoA reductase inhibitors (for example, rosuvastatin, atrovastatin, simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin and like), cholesterol-lowering drugs (for example, fibrates which include: fenofibrate, benzafibrate, clofibrate, gemfibrozil and like; cholesterol absorption inhibitors such as Ezetimibe, eflucimibe and like compounds), cholesterol ester transfer protein inhibitors (for example, CP-529414, CETi-1, JTT-705 and like compounds), bile acid sequestrants (for example, cholestyramine, colestipol, and like compounds), niacin, microsomal triglyceride transfer protein inhibitors (for example, implitapide), insulin signaling

pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases) and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), inhibitors of glucose-6-phosphatase (G6 Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase, glucagon receptor antagonists, inhibitors of phosphoenolpyruvate carboxylase (PEPCK), inhibitors of pyruvate dehydrogenase kinase, activators AMP-activated protein kinase (AMPK), (*R*)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}2,3-dihydro-l*H*-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, and GI-262570.

[0183] For the treatment of obesity, compounds according to the present invention may be administered with an agent selected from the group comprising: cholescystokinin-A (CCK-A) agonists, serotonin and norepinephrine reuptake inhibitors (for example sibutramine), dopamine agonists (for example, bromocriptine and like) sympathomimetic agents, β3 adrenergic receptor agonists, leptin, leptin analogues, leptin receptor agonists, galanin antagonists, lipase inhibitors (for example Orlistat), Neuropeptide-Y antagonists, glucocorticoid receptor agonists or antagonists, cannabinoid 1 receptor antagonists (for example, rimonabant and like), ciliary neurotropic factors (CNTF, for example Axokine), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists, appetite suppressants (for example, bupropion), urocortin binding protin antagonists, orexin receptor antagonists, and bombesin agonists.

[0184] For the treatment of inflammatory diseases , compounds according to the present invention may be administered with an agent selected from the group comprising: corticosteroids, non-steroidal anti-inflammatories, muscle relaxants and combinations thereof with other agents, anaesthetics and combinations thereof with other agents, expectorants and combinations thereof with other agents, antidepressants, anticonvulsants and combinations thereof; antihypertensives, opioids, topical cannabinoids, and other agents, such as capsaicin.

[0185] For the treatment of inflammatory diseases, compounds according to the present invention may be administered with an agent selected from the group comprising: betamethasone dipropionate (augmented and nonaugemnted),

betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream (Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%), guaifenesin, guaifenesin/ketoprofen/cyclobenzaprine, amitryptiline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, carbamazepine/cyclobenzaprine, antihypertensives including clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil; CB1/CB2 ligands, acetaminophen, infliximab; n) nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide synthase; anti-TNFα agents including, but not limited to etanerecept and infliximab, and other agents, such as capsaicin.

[0186] In any case, the multiple therapeutic agents (at least one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[0187] Thus, in another aspect, certain embodiments provide methods for treating TGR5-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound disclosed herein effective to reduce or prevent said disorder in the subject, in combination with at least

one additional agent for the treatment of said disorder that is known in the art. In a related aspect, certain embodiments provide therapeutic compositions comprising at least one compound disclosed herein in combination with one or more additional agents for the treatment of TGR5-mediated disorders.

[0188] Specific diseases to be treated by the compounds, compositions, and methods disclosed herein include: diabetes (type I and type II) and conditions associated with diabetic diseases which include, but are not limited to, hyperglycemia, hyperlipidemia, hyperinsulinemia, insulin resistance, inadequate glucose tolerance, impaired glucose metabolism, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, macular degeneration, diabetic retinopathy, chronic microvascular complications, peripheral vascular disease, cataracts, stroke, foot ulcerations, renal failure, kidney disease, ketosis, metabolic acidosis, and related disorders, obesity, myocardial infarction, angina pectoris, coronary artery disease, atherosclerosis, cardiac hypertrophy, allergic diseases, fatty liver disease, nonalcoholic steatohepatitis, liver fibrosis, kidney fibrosis, anorexia nervosa, bulimia vervosa, autoimmune diseases, inflammatory diseases including rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), psoriasis, ulcerative colitis, proliferative disorders, infectious diseases, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation, and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

[0189] In certain aspects of the invention, the disease is obesity and the effects to be achieved in a human or animal patient include decreasing body weight and controlling weight gain.

[0190] In certain aspects of the invention, the disease is associated with perturbed bile acid metabolism, including, but not limited to gall bladder stones, cholecystitis, cholangitis, choledocholithiasis, jaundice, and obstetric cholestasis and the itch associated with it.

[0191] In certain aspects of the invention, the disease is a hyperproliferative condition of the human or animal body, including, but not limited to restenosis, inflammation, immune disorders, cardiac hypertrophy, atherosclerosis, pain, migraine,

angiogenesis-related conditions or disorders, proliferation induced after medical conditions, including but not limited to surgery, angioplasty, or other conditions.

[0192] The compositions of the present invention are useful as anti-inflammatory agents with the additional benefit of having significantly less harmful side effects. The compositions are useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis. The compositions may also be used in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The invention further extends to the particular inflammatory disease rheumatoid arthritis.

[0193] Further inflammatory diseases which may be prevented or treated include, without limitation: asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis. Furthermore, respiratory system diseases may be prevented or treated including but not limited to chronic obstructive pulmonary disease, pulmonary fibrosis, ulcerative colitis, inflammatory bowel disease, Crohn's disease, peptic ulceration, gastritis, psoriasis, and skin inflammation.

[0194] In some aspects of the invention, the disease to be treated by the methods of the present invention may be an ophthalmologic disorder. Ophthalmologic diseases and other diseases in which angiogenesis plays a role in pathogenesis, may be treated or prevented and include, without limitation, dry eye (including Sjögren's syndrome), macular degeneration, closed and wide angle glaucoma, retinal ganglion degeneration, occular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. The compositions can be used to treat glaucomatous retinopathy and/or diabetic retinopathy. The compositions can also be used to treat post-operative inflammation or pain as from ophthalmic surgery such as cataract surgery and refractive surgery.

[0195] In some aspects of the invention, the disease to be treated by the methods of the present invention may be an autoimmune disease. Autoimmune diseases which may be prevented or treated include, but are not limited to: rheumatoid arthritis, inflammatory bowel disease, inflammatory pain, ulcerative colitis, Crohn's disease,

periodontal disease, temporomandibular joint disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs. host disease, and psoriasis. Inflammatory diseases which may be prevented or treated include, but are not limited to: asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis. The invention further extends to the particular autoimmune disease rheumatoid arthritis.

[0196] Metabolic diseases which may be treated or prevented include, without limitation, metabolic syndrome, insulin resistance, and Type 1 and Type 2 diabetes. In addition, the compositions of the subject invention can be used to treat insulin resistance and other metabolic disorders such as atherosclerosis that are typically associated with an exaggerated inflammatory signaling.

[0197] The compositions of the present invention are also useful in treating tissue damage in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephritis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, periodontis, hypersensitivity, swelling occurring after injury, ischemias including myocardial ischemia, cardiovascular ischemia, and ischemia secondary to cardiac arrest, and the like. These compositions can also be used to treat allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and atherosclerosis.

[0198] In some aspects of the invention, the disease to be treated by the methods of the present invention may be a cardiovascular condition. In certain embodiments, said cardiovascular condition is selected from the group consisting of atherosclerosis, cardiac hypertrophy, idiopathic cardiomyopathies, heart failure, angiogenesis-related conditions or disorders, and proliferation induced after medical conditions, including, but not limited to restenosis resulting from surgery and angioplasty.

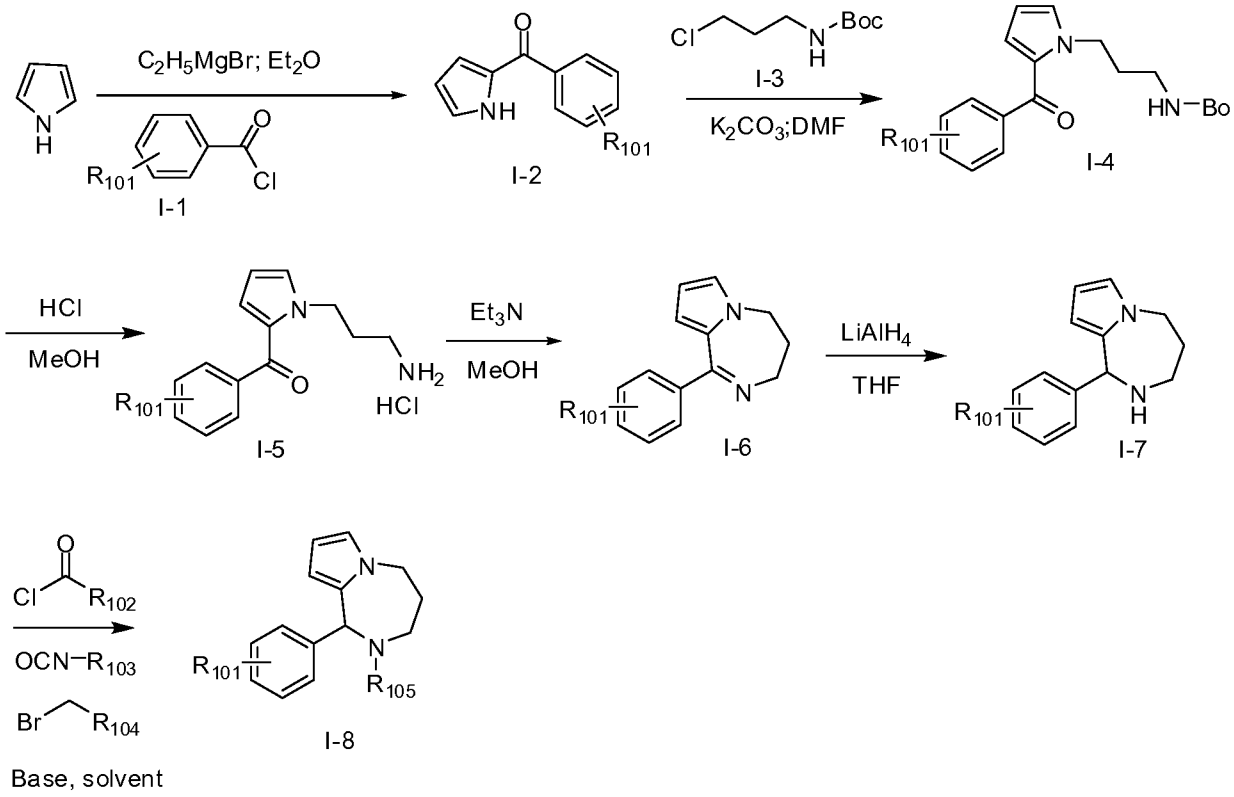
[0199] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion

animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

General Synthetic Methods for Preparing Compounds

[0200] The following schemes can be used to practice the present invention. Starting materials are commercially available, made by known procedures, or prepared as illustrated herein.

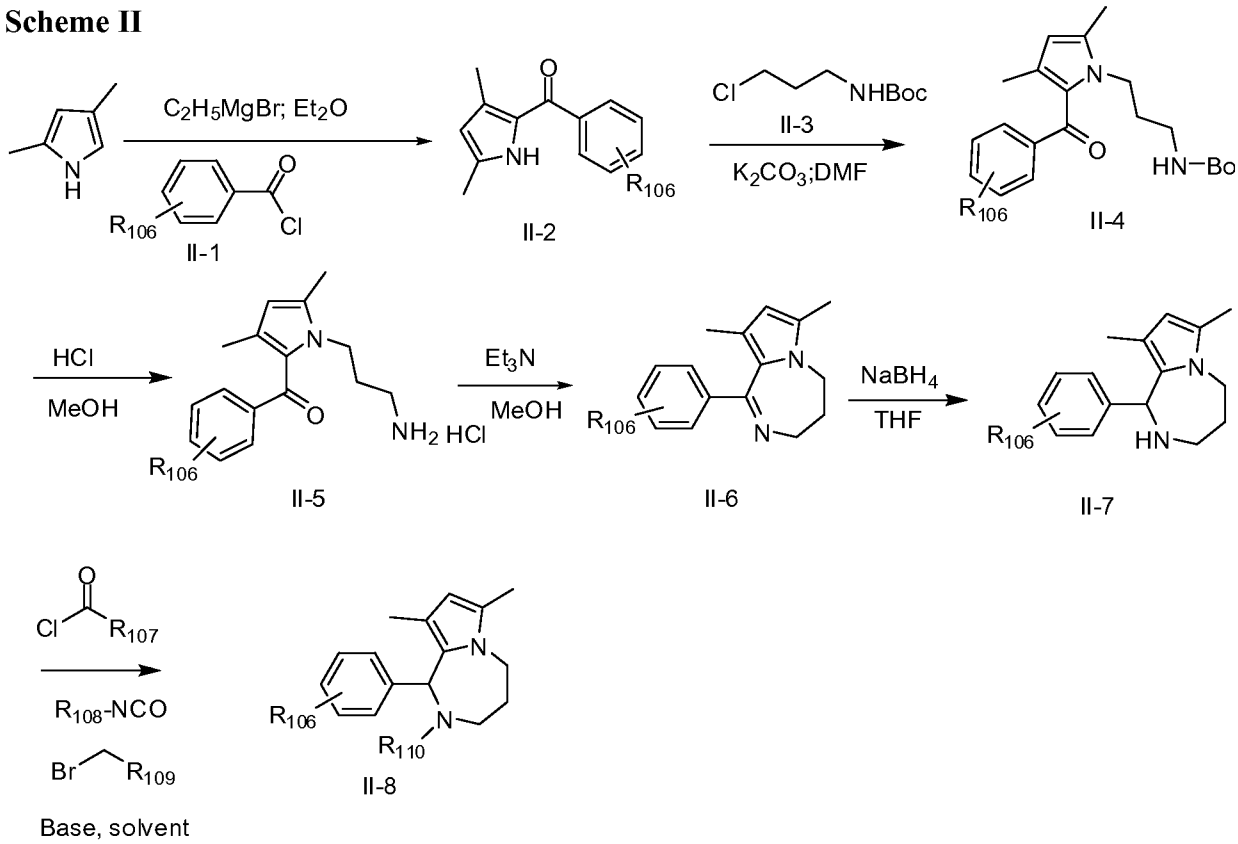
Scheme I



[0201] Examples 1-10 can be synthesized using the general synthetic procedure set forth in Scheme I: Pyyrole is reacted with ethylmagnesium bromide followed by an acid chloride I-1 to give compound I-2. Compound I-2 is then alkylated with chloride I-3 using standard conditions to give Boc protected compound I-4, which is then deprotected using acid to give compound I-5. Compound I-5 is then cyclized to give compound I-6, which is further reduced to diazepine derivative I-7. Diazepine

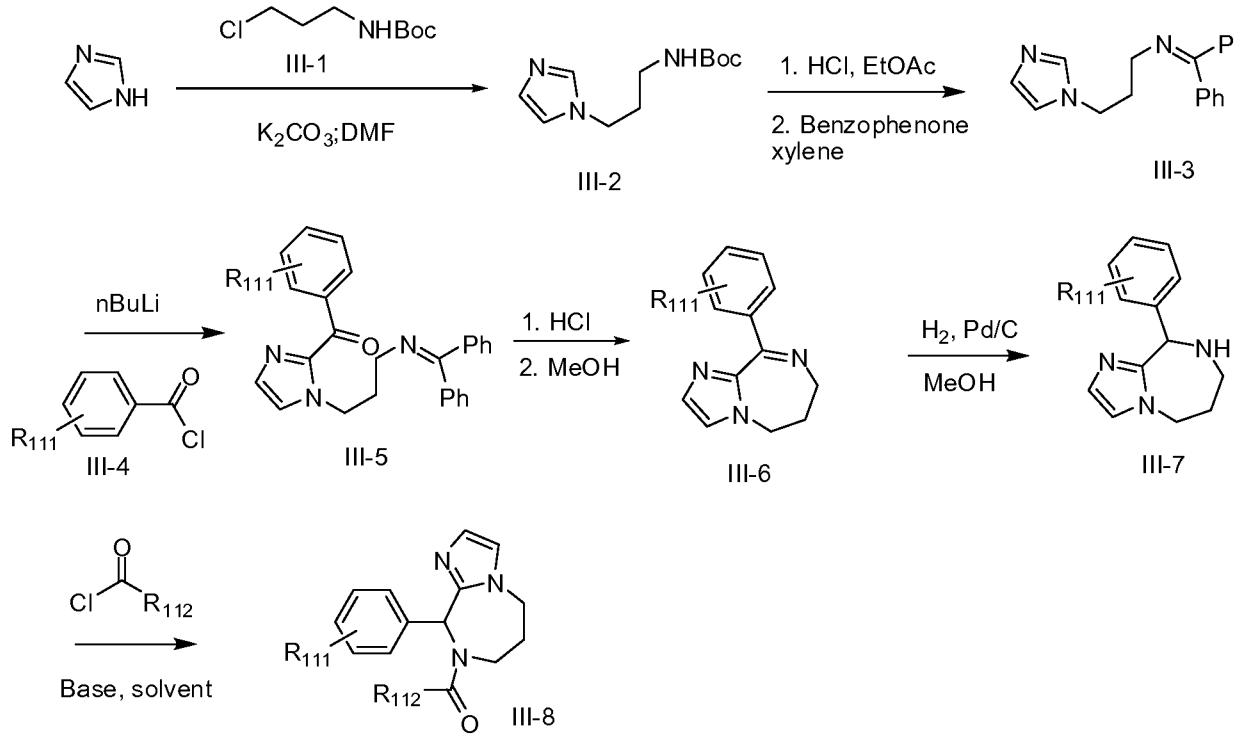
derivative I-7 is then further reacted with an acid chloride, benzyl bromide or isocyanate to give desired compound I-8. These compounds can exist as mixtures of stereoisomers. These can be separated by a variety of methods, including by HPLC using a column with a chiral stationary phase.

Scheme II



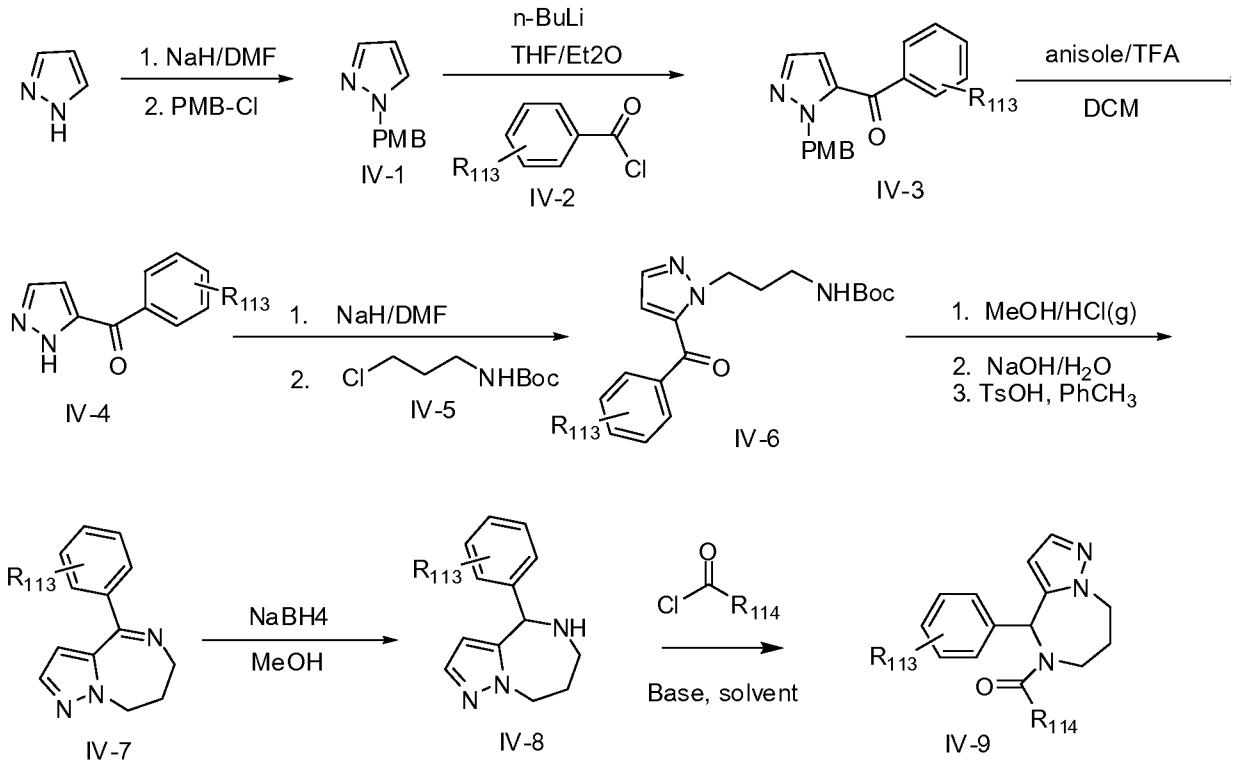
[0202] Example 11 can be synthesized using the general synthetic procedure set forth in Scheme II: 2,4-Dimethylpyrrole is reacted with ethylmagnesium bromide followed by an acid chloride II-1 to give compound II-2. Compound II-2 is then alkylated with chloride II-3 using standard conditions to give Boc protected compound II-4, which is then deprotected using acid to give compound II-5. Compound II-5 is then cyclized to give compound II-6, which is further reduced to diazepine derivative II-7. Diazepine derivative II-7 is then further reacted with an acid chloride, benzyl bromide or isocyanate to give desired compound II-8. These compounds can exist as mixtures of stereoisomers. These can be separated by a variety of methods, including by HPLC using a column with a chiral stationary phase.

Scheme III



[0203] Example 12 can be synthesized using the general synthetic procedure set forth in Scheme III: Imidazole is alkylated with chloride III-1 to give functionalized imidazole III-2. The Boc group of III-2 is then removed with acid and reprotected to give benzophenone imine III-3. The imidazole of compound III-3 is then deprotonated with n-butyllithium and reacted with acid chloride III-4 to give compound III-5. The benzophenone group of III-5 is then removed using HCl and compound III-6 is formed by stirring in methanol. Compound III-6 is then further reduced to give diazepine III-7 which is then reacted with an acid chloride to give the desired compound III-8. These compounds can exist as mixtures of stereoisomers. These can be separated by a variety of methods, including by HPLC using a column with a chiral stationary phase.

Scheme IV

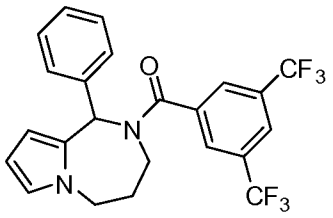


[0204] Example 13 can be synthesized using the general synthetic procedure set forth in Scheme IV: Pyrazole is protected with para-methoxybenzyl (PMB) to give compound IV-1. Compound IV-1 is then metallated with butyllithium and reacted with an acid chloride IV-2 to give pyrazole IV-3. The PMB group is then removed to give compound IV-4, which is then alkylated with chloride IV-5 to give compound IV-6. The Boc group is then removed with acid and the compound cyclized to give compound IV-7. Compound IV-7 is then reduced to give diazepine IV-8 which is reacted with an acid chloride to give desired compounds IV-9. These compounds can exist as mixtures of stereoisomers. These can be separated by a variety of methods, including by HPLC using a column with a chiral stationary phase.

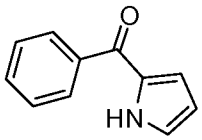
[0205] The invention is further illustrated by the following examples.

EXAMPLE 1

(3,5-bis(trifluoromethyl)phenyl)(1-phenyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone

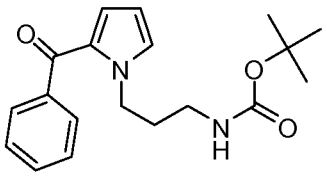


Step 1



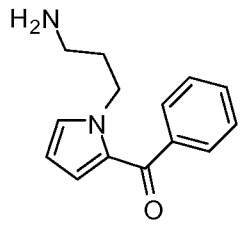
[0206] **Phenyl(1H-pyrrol-2-yl)methanone:** Into a 250 ml roundbottom flask was placed a solution of ethylmagnesium bromide (16.7 g, 125.28 mmol, 1.00 equiv) in ether (40 ml). This was followed by the addition of a solution of 1H-pyrrole (8.4 g, 125.30 mmol, 1.00 equiv) in ether (40 ml), which was added dropwise with stirring, while the temperature was maintained at reflux. The resulting solution was allowed to react for 0.5 hours while the temperature was maintained at reflux. It was then cooled to room temperature and a solution of benzoyl chloride (21 g, 150.00 mmol, 1.20 equiv) in ether (40 ml), was added dropwise over 1.5 hours. The resulting solution was stirred for 24 hr, then quenched by adding 100 ml of ammonium chloride. The resulting solution was extracted two times with 100 ml of ether and the organic layers combined. The resulting mixture was washed once with 50 ml of NaCl (aq). The mixture was dried over magnesium sulfate and concentrated by evaporation under vacuum using a rotary evaporator. The residue was purified by eluting through a column with a 1:20 EtOAc/PE solvent system. This resulted in 8.4 g (crude) of phenyl(1H-pyrrol-2-yl)methanone as a light yellow solid.

Step 2



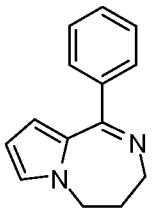
[0207] **Tert-butyl 3-(2-benzoyl-1H-pyrrol-1-yl)propylcarbamate:** Into a 100 ml roundbottom flask was placed a solution of phenyl(1H-pyrrol-2-yl)methanone (3.42 g, 20.00 mmol, 1.00 equiv) in DMF (40 ml). To this was added tert-butyl 3-chloropropylcarbamate (4.65 g, 24.01 mmol, 1.20 equiv) followed by potassium carbonate (22 g, 159.42 mmol, 8.00 equiv). The reaction was then heated to 90 °C and stirred overnight. It was then cooled to room temperature and diluted with 200 ml of water. The resulting solution was extracted three times with 100 ml of ethyl acetate and the organic layers combined. The resulting mixture was washed two times with 50 ml of NaCl (aq). The mixture was dried over magnesium sulfate and concentrated by evaporation under vacuum using a rotary evaporator. The crude tert-butyl 3-(2-benzoyl-1H-pyrrol-1-yl)propylcarbamate was taken immediately to the next step.

Step 3



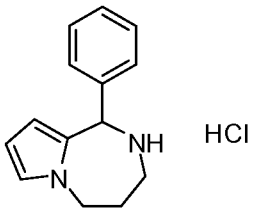
[0208] **(1-(3-Aminopropyl)-1H-pyrrol-2-yl) (phenyl)methanone:** Into a 500 ml 3-necked roundbottom flask was placed a solution of tert-butyl 3-(2-benzoyl-1H-pyrrol-1-yl) propylcarbamate (3 g, 1.00 equiv, crude) in ethyl acetate (200 ml). HCl was bubbled into the mixture for 10 min. The resulting solution was stirred for 4 hours while the temperature was maintained at room temperature. The pH to was then adjusted to 8-9 by the addition of ammonium hydroxide. The resulting solution was extracted three times with 100 ml of ethyl acetate and the organic layers combined and dried over sodium sulfate and concentrated by evaporation under vacuum using a rotary evaporator. The crude (1-(3-aminopropyl)-1H-pyrrol-2-yl) (phenyl)methanone was taken immediately to the next step.

Step 4



[0209] **(Z)-1-Phenyl-4,5-dihydro-3H-pyrrolo[1,2-a][1,4]diazepine:** Into a 100 ml roundbottom flask was placed a solution of (1-(3-aminopropyl)-1H-pyrrol-2-yl) (phenyl)methanone (4 g, 1.00 equiv, crude) in EtOH (50 ml). The resulting solution was stirred overnight while the temperature was maintained at reflux. The mixture was concentrated by evaporation under vacuum using a rotary evaporator to give (Z)-1-phenyl-4,5-dihydro-3H-pyrrolo[1,2-a][1,4]diazepine as brown oil.

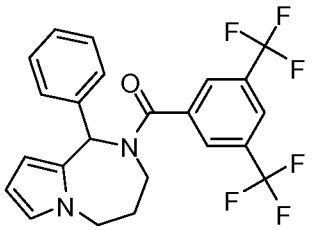
Step 5



[0210] **1-Phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4] diazepine hydrochloride:** Into a 50 ml roundbottom flask was placed a solution of (Z)-1-phenyl-4,5-dihydro-3H-pyrrolo[1,2-a][1,4] diazepine (1.6 g, 7.62 mmol, 1.00 equiv) in MeOH(30 ml). To this was added sodium borohydride (300 mg, 7.89 mmol, 1.10 equiv). The resulting solution was stirred for 3 hours while the temperature was maintained at room temperature. The mixture was concentrated by evaporation under vacuum using a rotary evaporator. The reaction was tehn diluted with 150 ml of water. The resulting solution was extracted three times with 60 ml of ether and the organic layers combined and dried over magnesium sulfate. HCl gas was then bubbled through the solution and the resulting solid collected via filtration. This resulted in 1.8 g (92%)

of 1-phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4] diazepine hydrochloride as a pink solid.

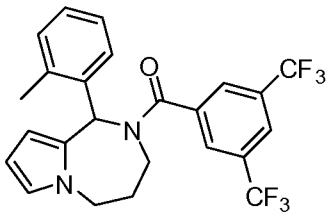
Step 6



[0211] **(3,5-bis(trifluoromethyl)phenyl)(1-phenyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone:** 3,5-Bis-trifluoromethylphenylcarbonyl chloride (138 mg, 0.5 mmol) was added to a solution of 1-phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4] diazepine hydrochloride (106 mg, 0.5 mmol) and triethylamine (126 mg, 1.25 mmol) in methylene chloride (5 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-bis(trifluoromethyl)phenyl)(1-phenyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as a colorless gum.
^{1}H NMR (500 MHz, $CDCl_3$): 7.94-7.90 (m, 3H), 7.41-7.27 (m, 4H), 7.07-6.90 (m, 1H), 6.71-6.69 (m, 2H), 6.26-6.08 (m, 1H), 5.97-5.77 (m, 1H), 4.86-4.82 (m, 0.5H), 4.15-4.09 (m, 1.5H), 3.95-3.86 (m, 1H), 3.62-3.57 (m, 0.25H), 3.38-3.31 (m, 0.25H), 3.06-3.00 (m, 0.5H), 2.35-1.80 (m, 2H).
MS (ESI) 454.15 ($M+H^+$).

EXAMPLE 2

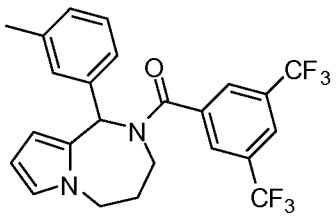
(3,5-bis(trifluoromethyl)phenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone



[0212] A similar procedure to Example 1 was followed. 3,5-Bis-trifluoromethylphenylcarbonyl chloride (124 mg, 0.45 mmol) was added to a solution of 1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine (85 mg, 0.38 mmol) and triethylamine (115 mg, 1.14 mmol) in methylene chloride (5 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-bis(trifluoromethyl)phenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as a red oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.87 (s, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 7.25-7.18 (m, 4H), 7.12-7.10 (m, 1H), 6.90-6.88 (m, 1H), 6.70-6.78 (m, 1H), 6.10-6.03 (m, 1H), 5.81 (m, 0.5H), 5.49 (m, 0.5H), 4.74-4.70 (m, 0.5H), 4.18-4.11 (m, 1.5H), 3.57-3.54 (m, 0.25H), 3.20-3.18 (m, 0.25H), 2.97-2.90 (m, 0.5H), 2.43 (m, 1.5H), 2.30-2.21 (m, 1H), 2.01 (s, 1.5H), 1.99-1.89 (m, 1H).
MS (ESI) 468.01 ($M+H^+$)

EXAMPLE 3

(3,5-bis(trifluoromethyl)phenyl)(1-m-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone



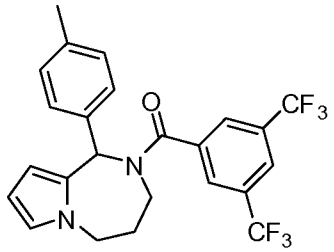
[0213] A similar procedure to Example 1 was followed. 3,5-Bis-trifluoromethylphenylcarbonyl chloride (277 mg, 1 mmol) was added to a solution of 1-m-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine (226 mg, 1 mmol) and triethylamine (252 mg, 2.5 mmol) in methylene chloride (10 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-bis(trifluoromethyl)phenyl)(1-m-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as an orange oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.94-7.90 (m, 3H), 7.30.7.09 (m, 3H), 6.71-6.69 (m, 3H), 6.14-6.08 (m, 1H), 5.92 (m, 1H), 5.76 (m, 1H), 4.85-4.82 (m, 0.5H), 4.13-4.09 (m, 1H),

3.97-3.87 (m, 0.5 H), 3.60 -3.56 (m, 0.25H), 3.39-3.32 (m, 0.25H), 3.08-3.02 (m, 0.5H), 2.21 (s, 3H), 2.10-1.90 (m, 2H).

MS (ESI) 467.30 ($M+H^+$)

EXAMPLE 4

(3,5-bis(trifluoromethyl)phenyl)(1-p-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone



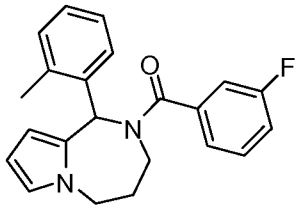
[0214] A similar procedure to Example 1 was followed. 3,5-Bis-trifluoromethylphenylcarbonyl chloride (138 mg, 0.5 mmol) was added to a solution of 1-p-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine (113 mg, 0.5 mmol) and triethylamine (126 mg, 1.25 mmol) in methylene chloride (5 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-bis(trifluoromethyl)phenyl)(1-p-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as a colorless gum.

^1H NMR (500 MHz, $CDCl_3$): 7.94-7.89 (m, 3H), 7.19-7.13 (m, 2H), 6.97-6.92 (m, 1H), 6.79-6.68 (m, 3H), 6.25-6.07 (m, 2H), 5.92-5.76 (m, 1H), 4.84-4.81 (m, 0.5H), 4.13-4.07 (m, 1.5H), 3.96-3.86 (m, 1H), 3.59-3.55 (m, 0.25H), 3.38-3.36 (m, 0.25H), 3.07-3.01 (m, 0.5H), 2.33 (s, 3H), 2.25-1.80 (m, 1H).

MS (ESI) 468.23 ($M+H^+$).

EXAMPLE 5

(3-fluorophenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone



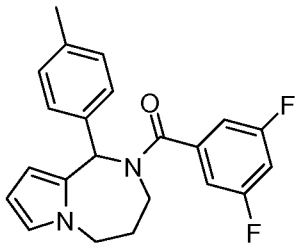
[0215] A similar procedure to Example 1 was followed. 3-Fluorophenylcarbonyl chloride (70 mg, 0.44 mmol) was added to a solution of 1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine hydrochloride (100 mg, 0.44 mmol) and triethylamine (110 mg, 1.1 mmol) in methylene chloride (5 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3-fluorophenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): 7.40-6.85 (m, 8H), 6.67-6.64 (m, 1H), 6.06-6.01 (m, 1H), 5.95-5.90 (m, 1H), 4.74-4.68 (m, 0.5H), 4.13-4.04 (m, 2H), 3.72-3.67 (m, 0.5H), 3.12-3.05 (m, 1 H), 2.42 (s, 3H), 1.95-1.69 (m, 3H).

MS (ESI) 349.79 ($M+H^+$).

EXAMPLE 6

(3,5-difluorophenyl)(1-p-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone

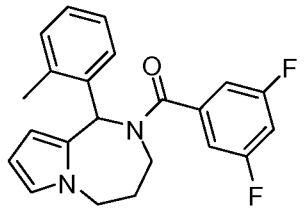


[0216] A similar procedure to Example 1 was followed. 3,5-difluorophenylcarbonyl chloride (88 mg, 0.5 mmol) was added to a solution of 1-p-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine (113 mg, 0.5 mmol) and triethylamine (126 mg, 1.25 mmol) in methylene chloride (5 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-difluorophenyl)(1-p-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as a colorless gum.

^{1}H NMR (500 MHz, $CDCl_3$): 7.60-7.56 (m, 1H), 7.15-7.13 (m, 2H), 7.06-6.80 (m, 5H), 6.67-6.64 (m, 1H), 6.21-6.05 (m, 2H), 5.80-5.79 (m, 1H), 4.80-4.76 (m, 0.5H), 4.11-4.04 (m, 1.5H), 3.93-3.81 (m, 1H), 3.70-3.66 (m, 0.25H), 3.32-3.25 (m, 0.25H), 3.05-2.99 (m, 0.5H), 2.33 (s, 3H), 2.25-1.74 (m, 1H).
MS (ESI) 368.18 ($M+H^+$).

EXAMPLE 7

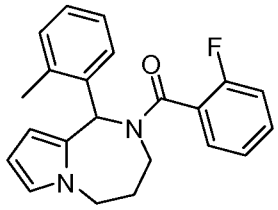
(3,5-difluorophenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone



[0217] A similar procedure to Example 1 was followed. 3,5-Difluorophenylcarbonyl chloride (78 mg, 0.44 mmol) was added to a solution of 1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine hydrochloride (100 mg, 0.44 mmol) and triethylamine (110 mg, 1.1 mmol) in methylene chloride (5 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-difluorophenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.59-7.57 (m, 0.5H), 7.25-6.65 (m, 6.5H), 6.07-6.03 (m, 1H), 5.94-5.91 (m, 2H), 4.71-4.66 (m, 0.5H), 4.13-4.06 (m, 2H), 3.3.69-3.65 (m, 0.5H), 3.17-2.85 (m, 1 H), 2.40 (s, 3H), 2.21-2.18 (m, 1H), 1.99-1.74 (m, 2H).
MS (ESI) 368.19 ($M+H^+$).

EXAMPLE 8

(2-fluorophenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone



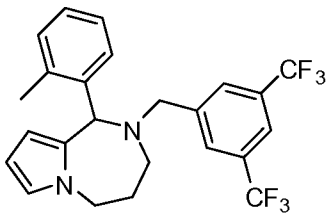
[0218] A similar procedure to Example 1 was followed. 2-Fluorophenylcarbonyl chloride (70 mg, 0.44 mmol) was added to a solution of 1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine hydrochloride (100 mg, 0.44 mmol) and triethylamine (110 mg, 1.1 mmol) in methylene chloride (5 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (2-fluorophenyl)(1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): 8.00-7.96 (m, 0.5H), 7.56-7.51 (m, 0.5H), 7.39-6.93 (m, 7H), 6.65-6.62 (m, 1H), 6.05-5.84 (m, 2H), 4.79-4.74 (m, 0.5H), 4.25-4.05 (m, 2H), 3.62-3.58 (m, 0.5H), 3.17-2.99 (m, 1 H), 2.43 (s, 3H), 1.91-1.65 (m, 3H).

MS (ESI) 350.20 ($M+H^+$).

EXAMPLE 9

2-(3,5-bis(trifluoromethyl)benzyl)-1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine



[0219] A similar procedure to Example 1 was followed. 3,5-Bistrifluoromethylbenzylbromide (203 mg, 0.66 mmol) was added to a solution of 1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine hydrochloride (100 mg, 0.44 mmol) and potassium carbonate (152 mg, 1.1 mmol) in DMF (4 mL) at room temperature. The reaction was heated to 60 °C and stirred for 16 hr. It was then cooled to rt, poured into ethyl acetate, extracted 3 times with saturated sodium bicarbonate and dried over magnesium sulfate. The solvent was removed and the residue purified by silica gel column (0-100% ethyl acetate/hexanes) to give 2-(3,5-

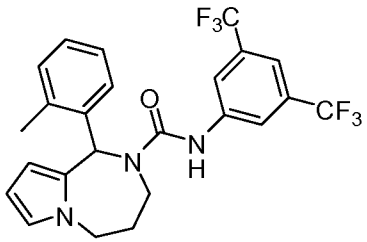
bis(trifluoromethyl)benzyl)-1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): 7.86-7.71 (m, 3H), 7.16-7.14 (m, 2H), 7.10-7.06 (m, 1H), 6.86-6.84 (m, 1H), 6.70-6.68 (m, 1H), 6.09 (t, 1H), 5.90 (m, 1H), 5.04 (s, 1H), 4.14-4.10 (m, 2H), 3.75 (q, 2H), 2.89-2.85 (m, 2H), 2.34 (s, 3H), 2.09-2.04 (m, 1H), 1.54-1.46 (m, 1H).

MS (ESI) 454.23 ($M+H^+$).

EXAMPLE 10

N-(3,5-bis(trifluoromethyl)phenyl)-1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepine-2(3H)-carboxamide



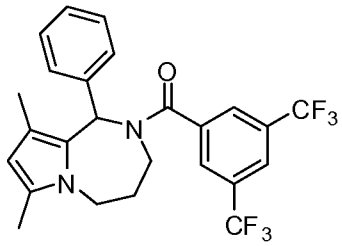
[0220] A similar procedure to Example 1 was followed. 3,5-Bistrifluoromethylphenylisocyanate (112 mg, 0.44 mmol) was added to a solution of 1-o-tolyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine hydrochloride (100 mg, 0.44 mmol) and triethylamine (67 mg, 0.66 mmol) in dichloromethane (5 mL) at room temperature. The reaction was stirred at room temperature overnight. It was then extracted with 1N HCl then saturated sodium bicarbonate and dried over magnesium sulfate. The solvent was removed and the residue purified by silica gel column (0-100% ethyl acetate/hexanes) to give N-(3,5-bis(trifluoromethyl)phenyl)-1-o-tolyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepine-2(3H)-carboxamide as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): 8.04-7.99 (m, 1H), 7.92-7.86 (m, 2H), 7.56-7.51 (m, 2H), 7.46 (m, 1H), 7.38-7.21 (m, 4H), 6.71-6.69 (m, 1H), 6.03 (t, 1H), 4.26-4.23 (m, 1H), 4.16-4.13 (m, 2H), 2.95-2.89 (m, 1H), 2.39 (s, 3H), 2.34-2.20 (m, 1H), 1.90-1.81 (m, 1H).

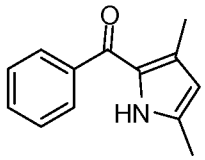
MS (ESI) 483.25 ($M+H^+$).

EXAMPLE 11

(3,5-bis(trifluoromethyl)phenyl)(7,9-dimethyl-1-phenyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone

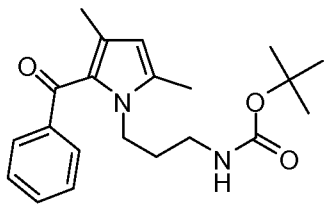


Step 1



[0221] **(3,5-Dimethyl-1H-pyrrol-2-yl)(phenyl)methanone:** To the stirred solution of ethylmagnesium bromide (12.6 g, 94.52mmol, 1.50 equiv) in Et_2O (40 ml) was added a solution of 2,4-dimethyl-1H-pyrrole (6 g, 63.16 mmol) in Et_2O (20ml) at reflux. After refluxing for 30minutes, the above mixture was added dropwise to a solution of benzoyl chloride (10.64, 76mmol, 1.20 equiv) in Et_2O (40 ml) at room temperature. After being stirred overnight, the reaction mixture was quenched with aqueous NH_4Cl (100ml). The mixture was extracted with ether (100ml×2). The combined organic layer was washed with brine (50ml), dried over anhydrous Na_2SO_4, concentrated *in vacuo* to afford the crude product, which was purified with column chromatography eluting with EtOAc/PE, resulting in pure (3,5-dimethyl-1H-pyrrol-2-yl)(phenyl)methanone (5.8 g, 46%) as a light yellow solid.

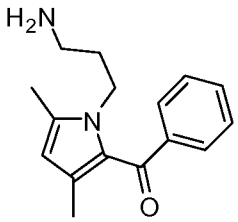
Step 2



[0222] **Tert-butyl 3-(2-benzoyl-3,5-dimethyl-1H-pyrrol-1-yl)propylcarbamate:** To a stirred solution of (3,5-dimethyl-1H-pyrrol-2-yl)(phenyl)methanone (2 g, 10.05 mmol) in DMF (50 ml) was added K_2CO_3 (13.8 g, 100.00 mmol, 10.00 equiv) tert-butyl 3-bromopropylcarbamate (2.86 g, 12.02 mmol, 1.20 equiv). The resulting

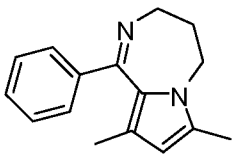
mixture was stirred overnight at 90 °C. It was then cooled to room temperature and quenched by H_2O (100ml). The resulting solution was extracted with EtOAc (100ml×3), and the combined organic layers was washed with brine (50ml), dried over Na_2SO_4 and concentrated *in vacuo* to afford crude product, which was purified by column chromatography eluting with EtOAc/PE, resulting in tert-butyl 3-(2-benzoyl-3,5-dimethyl-1H-pyrrol-1-yl)propylcarbamate (1.6 g, 44%) as a light yellow solid.

Step 3



[0223] **(1-(3-Aminopropyl)-3,5-dimethyl-1H-pyrrol-2-yl)(phenyl)methanone:** To a solution of tert-butyl 3-(2-benzoyl-3,5-dimethyl-1H-pyrrol-1-yl)propylcarbamate (2.1 g, 5.9mmol) in EtOAc (50ml) was bubbled into dry HCl gas at room temperature for 2h. After being stirred for another 2h, the pH was adjusted to 8-9 with ammonium hydroxide. The resulting solution was extracted with EtOAc (50 ml×3) and the combined organic layers were washed with brine (30ml), dried over Na_2SO_4 and concentrated *in vacuo* to give (1-(3-aminopropyl)-3,5-dimethyl-1H-pyrrol-2-yl)(phenyl)methanone (1.6 g), which was used in the next step without further purification.

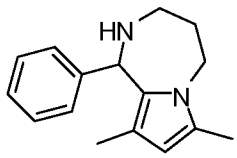
Step 4



[0224] **(Z)-7,9-Dimethyl-1-phenyl-4,5-dihydro-3H-pyrrolo[1,2-a][1,4]diazepine:** The intermediate (1-(3-aminopropyl)-3,5-dimethyl-1H-pyrrol-2-yl)(phenyl)methanone (2.1 g, 8.20 mmol) was dissolved in EtOH (100ml). After being refluxed overnight, the reaction was cooled to room temperature. The solvent was

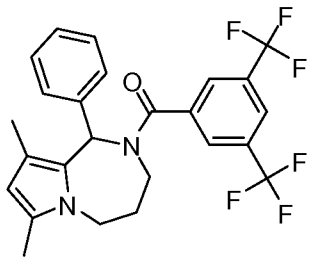
removed *in vacuo* to give (Z)-7,9-dimethyl-1-phenyl-4,5-dihydro-3H-pyrrolo[1,2-a][1,4]diazepine (1.4 g, crude) as yellow oil.

Step 5



[0225] **7,9-Dimethyl-1-phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine:** To the stirred solution of (Z)-7,9-dimethyl-1-phenyl-4,5-dihydro-3H-pyrrolo[1,2-a][1,4]diazepine (1.4 g, 5.88 mmol) in MeOH (40 ml) was added $NaBH_4$ (0.45 mg, 0.01 mmol, 2.00 equiv) in several batches at 0 degree. After being stirred at 0 degree, the reaction mixture was quenched by H_2O (50 ml). The resulting solution was extracted with EtOAc (30ml×3) and the combined organic layers were washed with brine (50ml), dried over Na_2SO_4, concentrated *in vacuo* to afford crude product, which was purified by column chromatography eluting with CH_2Cl_2/MeOH to produce pure product 7,9-dimethyl-1-phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine (0.6g, 42.8%) as a yellow solid.

Step 6



[0226] **(3,5-Bis(trifluoromethyl)phenyl)(7,9-dimethyl-1-phenyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone:** 3,5-Bis-trifluoromethylphenylcarbonyl chloride (49 mg, 0.18 mmol) was added to a solution of 7,9-dimethyl-1-phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine (33 mg, 0.14 mmol) and triethylamine (35 mg, 0.35 mmol) in methylene chloride (2 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-bis(trifluoromethyl)phenyl)(7,9-

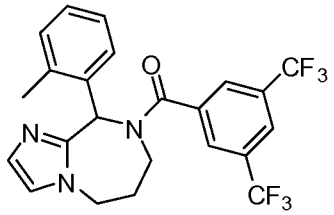
dimethyl-1-phenyl-4,5-dihydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): 8.52 (s, 1H), 7.94-7.89 (m, 2H), 7.40-7.29 (m, 3H), 7.07-7.00 (m, 2H), 5.98 (s, 1H), 5.67 (m, 1H), 4.78-4.73 (m, 1H), 4.14-4.06 (m, 1H), 3.62-3.54 (m, 1H), 3.13-3.07 (m, 1H), 2.23 (s, 3H), 1.97-1.72 (m, 2H), 1.40 (s, 3H).

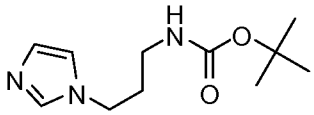
MS (ESI) 482.20 ($M+H^+$).

EXAMPLE 12

(3,5-bis(trifluoromethyl)phenyl)(9-o-tolyl-6,7-dihydro-5H-imidazo[1,2-a][1,4]diazepin-8(9H)-yl)methanone

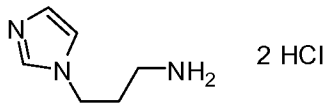


Step 1



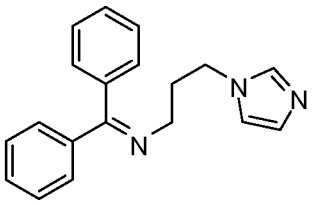
[0227] **Tert-butyl 3-(1H-imidazol-1-yl)propylcarbamate:** A mixture of tert-butyl 3-chloropropylcarbamate (11 g, 56.80 mmol, 1.00 equiv),1H-imidazole (5 g, 73.44 mmol, 1.29 equiv) and potassium carbonate (11 g) in DMF (100 ml) was stirred at room temperature for 2 days. The mixture was then mixed with 100 ml of ammonium chloride. The resulting solution was extracted three times with 100 ml of EtOAc and the organic layers combined and dried, then concentrated by evaporation. This resulted in 11 g of tert-butyl 3-(1H-imidazol-1-yl)propylcarbamate as yellow oil.

Step 2



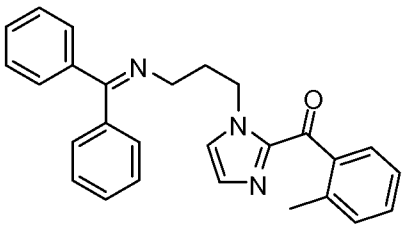
[0228] **3-(1H-Imidazol-1-yl)propan-1-amine dihydrochloride:** Tert-butyl 3-(1H-imidazol-1-yl)propylcarbamate (11 g, 48.83 mmol, 1.00 equiv) was dissolved in MeOH (100 ml). Then HCl gas was introduced with stirring for 6h at room temperature. The resulting solution was extracted three times with 100 ml of EtOAc and the organic layers combined and dried, concentrated by evaporation. This resulted in 8 g of 3-(1H-imidazol-1-yl)propan-1-amine dihydrochloride as yellow oil.

Step 3



[0229] **N-(Diphenylmethylene)-3-(1H-imidazol-1-yl)propan-1-amine:** A mixture of 3-(1H-imidazol-1-yl)propan-1-amine dihydrochloride (15 g, 75.76 mmol, 1.00 equiv) and benzophenone (30 g, 164.84 mmol, 1.00 equiv) in xylene (300 ml) was refluxed 36 hours. The solution was then concentrated by evaporation. This resulted in 17 g (77.6%)of N-(diphenylmethylene)-3-(1H-imidazol-1-yl)propan-1-amine as yellow oil.

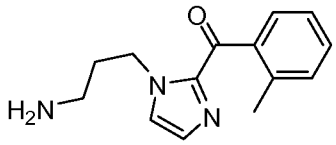
Step 4



[0230] **(1-(3-(Diphenylmethyleneamino)propyl)-1H-imidazol-2-yl)(o-tolyl)methanone:** To a –78°C mixture of N-(diphenylmethylene)-3-(1H-imidazol-1-yl)propan-1-amine (1.5 g, 5.19 mmol, 1.00 equiv) in 200ml THF was added n-BuLi (1.6 M, 2ml,1.00eq) dropwise. The resulting solution was allowed to react, with stirring, for 30 minutes while the temperature was maintained at -78°C , then 2-methylbenzoyl chloride (2 ml, 1.00 equiv) was added dropwise with stirring at -78°C.

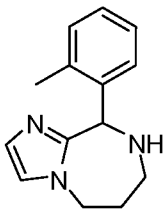
The reaction progress was then warmed to rt, and the resulting mixture quenched with 50 ml of ammonium chloride. The resulting solution was extracted two times with 100ml of EtOAc and the organic layers combined and dried over magnesium sulfate and concentrated. This resulted in 1 g (47%) of (1-(3-(diphenylmethyleneamino)propyl)-1H-imidazol-2-yl)(o-tolyl)methanone as yellow oil.

Step 5



[0231] **(1-(3-Aminopropyl)-1H-imidazol-2-yl)(o-tolyl)methanone:** (1-(3-(diphenylmethyleneamino)propyl)-1H-imidazol-2-yl)(o-tolyl)methanone (1 g, 2.45 mmol, 1.00 equiv) was dissolved in THF(10ml). To this was added HCl aqueous solution (10 ml). The resulting mixture was stirred for 6 hours at room temperature. Then, the pH was adjusted to 12 by the addition of 1N NaOH. The resulting solution was extracted two times with 100 ml of EtOAc and the organic layers combined, dried over magnesium sulfate and concentrated by evaporation. This resulted in 0.3 g of (1-(3-aminopropyl)-1H-imidazol-2-yl)(o-tolyl)methanone as a yellow solid. (1-(3-aminopropyl)-1H-imidazol-2-yl)(o-tolyl)methanone (300 mg, 1.23 mmol, 1.00 equiv) was dissolved in MeOH (10 ml). The resulting solution was stirred for 36 hours at room temperature. The mixture was then concentrated by evaporation. This resulted in 100 mg (36%) of (Z)-9-o-tolyl-6, 7-dihydro-5H-imidazo[1,2-a][1,4]diazepine as yellow oil.

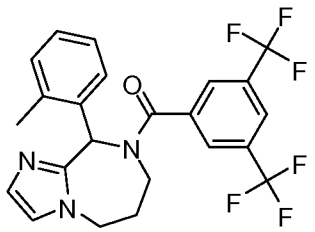
Step 6



[0232] **9-o-Tolyl-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,4]diazepine:** (Z)-9-o-tolyl-6,7-dihydro-5H-imidazo[1,2-a][1,4]diazepine (1 g, 4.44 mmol, 1.00 equiv) was

dissolved in MeOH (100 ml). To the mixture was added Pd/C (1.0 g). It was then stirred under 1 atm of hydrogen gas at room temperature for 8 hr. The mixture was then concentrated by evaporation and residue was purified by eluting through a silica gel column with a 1:1 methylene chloride/petroleum ether. This resulted in 1 g (79%) of 9-o-tolyl-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,4]diazepine as yellow oil.

Step 7



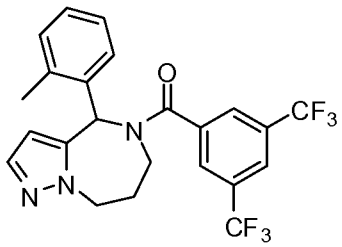
[0233] **(3,5-Bis(trifluoromethyl)phenyl)(9-o-tolyl-6,7-dihydro-5H-imidazo[1,2-a][1,4]diazepin-8(9H)-yl)methanone:** 3,5-Bis-trifluoromethylphenylcarbonyl chloride (182 mg, 0.66 mmol) was added to a solution of 9-o-tolyl-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,4]diazepine (150 mg, 0.66 mmol) and triethylamine (167 mg, 1.25 mmol) in methylene chloride (8 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-bis(trifluoromethyl)phenyl)(9-o-tolyl-6,7-dihydro-5H-imidazo[1,2-a][1,4]diazepin-8(9H)-yl)methanone as a yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$): 7.95-7.83 (m, 1H), 7.64-7.51 (m, 2H), 7.30-6.94 (m, 5H), 6.59-6.51 (m, 1H), 6.17 (m, 1H), 4.77-4.71 (m, 0.5H), 4.28-4.15 (m, 2.5H), 3.62-3.58 (m, 0.25H), 3.21-3.16 (m, 0.25H), 2.86-2.81 (m, 0.5H), 2.26-2.22 (m, 1H), 2.15 (s, 3H), 1.90-1.88 (m, 1H).

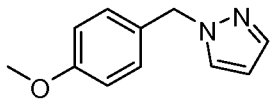
MS (ESI) 469.17 ($M+H^+$).

EXAMPLE 13

(3,5-bis(trifluoromethyl)phenyl)(4-o-tolyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)methanone

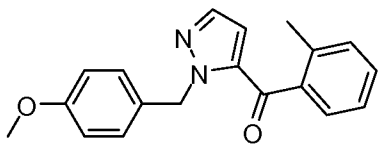


Step 1



[0234] **1-(4-Methoxybenzyl)-1H-pyrazole:** Into a 1000 ml 3-necked roundbottom flask was placed a solution of NaH (10.6 g, 265.00 mmol, 1.10 equiv, 60%) in DMF (400 ml). This was followed by the addition of a solution of 1H-pyrazole (27.2 g, 400.00 mmol, 1.00 equiv) in DMF (100 ml) dropwise over a time period of 1.5 hours. The resulting solution was allowed to react, with stirring, for 2 hours while the temperature was maintained at rt. This was followed by the addition of a solution of PMB-Cl (68.6 g, 439.74 mmol, 1.10 equiv) in DMF (100 ml) over a time period of 2 hours. The resulting solution was stirred overnight at room temperature. The reaction mixture was then quenched by the adding 1000 ml of water/ice. The resulting solution was extracted three times with 200 ml of ether and the organic layers combined and dried over magnesium sulfate. The residue was purified by eluting through a silica gel column with a 1:5 EtOAc/PE solvent system. This resulted in 40 g (53.1%) of 1-(4-methoxybenzyl)-1H-pyrazole as yellow oil.

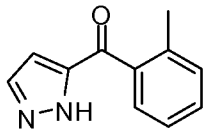
Step 2



[0235] **(1-(4-Methoxybenzyl)-1H-pyrazol-5-yl)(o-tolyl)methanone:** Into a 250 ml 3-necked roundbottom flask was placed a solution of 1-(4-methoxybenzyl)-1H-pyrazole (5 g, 26.56 mmol, 1.00 equiv) in THF/ether(3:2) (70 ml). This was followed

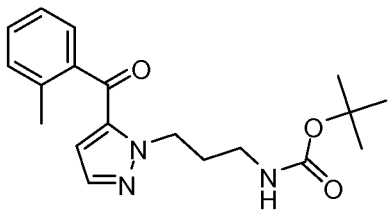
by the addition of a solution of n-BuLi (10.6 ml, 1.00 equiv, 2.5M) in THF/ether(3:2) (30 ml), which was added dropwise with stirring at -78 °C. The resulting solution was stirred for 1.5 hours while the temperature was maintained at -78 °C. This was followed by the addition of a solution of 2-methylbenzoyl chloride (4.31 g, 27.88 mmol, 1.05 equiv) in THF/ether(3:2) (10 ml), which was added dropwise at -78 °C. The resulting solution was stirred for an additional 4 hours while the temperature was maintained at -78 °C. Then the resulting solution was stirred overnight at room temperature. Then 800 ml of water was added and the reaction was extracted three times with 200 ml of EtOAc, the organic layers combined and dried over magnesium sulfate and concentrated by evaporation under vacuum using a rotary evaporator. The residue was purified by eluting through a silica gel column with a 1:30 EtOAc/PE solvent system. This resulted in 2.2 g (27.2%) of (1-(4-methoxybenzyl)-1H-pyrazol-5-yl)(o-tolyl)methanone as colourless oil.

Step 3



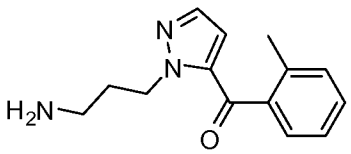
[0236] **(1H-Pyrazol-5-yl)(o-tolyl)methanone:** Into a 500 ml 3-necked roundbottom flask was placed a solution of (1-(4-methoxybenzyl)-1H-pyrazol-5-yl)(o-tolyl)methanone (2.2 g, 7.19 mmol, 1.00 equiv) in dichloroethane (200 ml). To this was added anisole (7.76 g, 71.85 mmol, 10.00 equiv) then TFA (4.09 g, 35.88 mmol, 5.00 equiv). The resulting solution was stirred overnight at reflux. The mixture was then cooled to room temperature and concentrated by evaporation under vacuum using a rotary evaporator. The residue was purified by eluting through a silica gel column with a 1:20 EtOAc/PE solvent system. This resulted in 1.13 g(86.9%) of (1H-pyrazol-5-yl)(o-tolyl)methanone as colorless oil.

Step 4



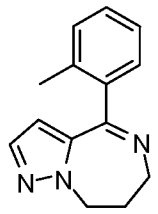
[0237] **Tert-butyl 3-(5-(2-methylbenzoyl)-1H-pyrazol-1-yl)propylcarbamate:** Into a 250 ml 3-necked roundbottom flask was placed a solution of NaH (368 mg, 15.33 mmol, 1.50 equiv) in DMF (100 ml). To this was added (1H-pyrazol-5-yl)(o-tolyl)methanone (1.13 g, 6.08 mmol, 1.00 equiv). To the mixture was added tert-butyl 3-bromopropylcarbamate (920 mg, 3.88 mmol, 1.50 equiv). The resulting solution was stirred overnight at room temperature. The reaction mixture was then quenched by adding 200 ml of water. The resulting solution was extracted three times with 300 ml of EtOAc and the organic layers combined and dried over sodium sulfate and concentrated by evaporation under vacuum using a rotary evaporator. The residue was purified by eluting through a silica gel column with a 1/10 EtOAc/PE solvent system. This resulted in 0.3 g (14.3%) of tert-butyl 3-(5-(2-methylbenzoyl)-1H-pyrazol-1-yl)propylcarbamate as yellow oil.

Step 5



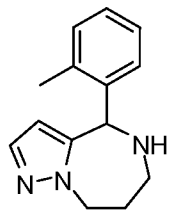
[0238] **(1-(3-Aminopropyl)-1H-pyrazol-5-yl)(o-tolyl)methanone:** Into a 250 ml 3-necked roundbottom flask was placed a solution of tert-butyl 3-(5-(2-methylbenzoyl)-1H-pyrazol-1-yl)propylcarbamate (2.4 g, 7.00 mmol, 1.00 equiv) in methanol (100 ml). To the above was bubbled HCl(gas) for 1 hour. The resulting solution was stirred for 30 minutes while the temperature was maintained at 0 °C. The pH was then adjusted to 10-12 with the addition of sodium carbonate. The resulting solution was extracted five times with 100ml of methylene chloride, dried over magnesium sulfate and concentrated by evaporation under vacuum using a rotary evaporator. This resulted in 1.2 g of (1-(3-aminopropyl)-1H-pyrazol-5-yl)(o-tolyl)methanone as yellow oil.

Step 6



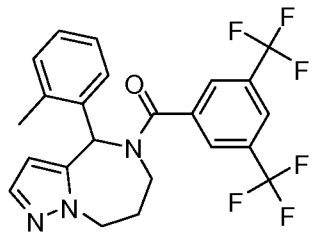
[0239] **(Z)-4-o-Tolyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,4]diazepine:** Into a 250 ml 3-necked roundbottom flask was placed a solution of (1-(3-aminopropyl)-1H-pyrazol-5-yl)(o-tolyl)methanone (700 mg, 2.88 mmol, 1.00 equiv) in toluene (100 ml). To the mixture was added TsOH (0.07 g, 0.10 equiv). The resulting solution was refluxed overnight. It was then cooled to room temperature and filtered. The filtrate was concentrated by evaporation under vacuum using a rotary evaporator. This resulted in 0.7 g of (Z)-4-o-tolyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,4]diazepine as a yellow solid.

Step 7



4-o-Tolyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine: Into a 100 ml roundbottom flask, was placed a solution of (Z)-4-o-tolyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,4]diazepine (700 mg, 3.11 mmol, 1.00 equiv) in MeOH (50 ml). To the mixture was added sodium borohydride (473 mg, 12.45 mmol, 4.00 equiv) in several batches. The resulting solution was stirred for 1 hr while the temperature was maintained at -20 °C. The reaction mixture was then quenched by the adding 50 ml of ammonium chloride. The resulting solution was extracted three times with 100 of EtOAc and the organic layers combined and dried over magnesium sulfate and concentrated by evaporation under vacuum using a rotary evaporator. This resulted in 200 mg(27.9%) of 4-o-tolyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine as a white solid.

Step 8



[0240] **(3,5-Bis(trifluoromethyl)phenyl)(4-o-tolyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)methanone:** 3,5-Bis-trifluoromethylphenylcarbonyl chloride (158 mg, 0.57 mmol) was added to a solution of 4-o-tolyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (100 mg, 0.44 mmol) and triethylamine (110 mg, 1.1 mmol) in methylene chloride (6 mL) at room temperature. The reaction was stirred for 1 hr, then applied directly to a silica gel column (0-100% ethyl acetate/hexanes) to give (3,5-bis(trifluoromethyl)phenyl)(4-o-tolyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)methanone as a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.96-7.94 (m, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.55-7.51 (m, 1H), 7.33-7.18 (m, 3H), 6.76 (t, 1H), 6.33-6.32 (m, 1H), 5.92-5.80 (m, 1H), 4.79-4.42 (m, 3H), 3.63-3.60 (m, 0.5H), 2.90-2.84 (m, 0.5H), 2.44 (s, 3H), 2.30-2.02 (m, 2H).
MS (ESI) 469.17 ($M+H^+$).

[0241] The activity of the compounds in Examples 1-13 as TGR5 modulators is illustrated in the following assays.

Biological Activity Assay

cAMP Production Assay:

[0242] HEK293 cells stably expressing TGR5 (HEK293-TGR5) were established by stably transfecting HEK-293 cells with an expression vector (pcDNA 3.1, Invetrogen) inserted with human TGR5 cDNA using Fugene6 (Roche, Indianapolis, IN) according to conventional methods. Cells were grown in DMEM (invitrogen, Carlsbad, CA) supplemented with 10% FBS, 1% penicillin/streptomycin under geneticin selection. The presence of TGR5 transcripts in these cells was confirmed

using branched DNA (bDNA, Genospectra, Inc., Fremont CA) following the manufacturer's protocol and using specific probes for human TGR5. cAMP production assay was performed in high throughput 1536 well format using LANCE cAMP detection kit (Perkin Elmer Inc., Boston, MA) according to the manufacturer's protocol. Briefly, HEK293-TGR5 cells were harvested using non-enzymatic cell dissociation buffer (Invitrogen, Carlsbad, CA) and suspended in DMEM supplemented with 0.1% FBS at a density of 800,000 cells/ml. Alexa antibody was added to the cell suspension, and 4 ul of the mixture was dispensed in white opaque tissue culture treated Greiner 1536 well plates (USA Scientific, Inc., Ocala, FL). After an overnight incubation at 37C in an atmosphere of 10% CO2 and 95% humidity, 1 ul of 5 mM IBMX (Sigma, St. Louis, MO) solution in DMEM was dispensed for a final concentration of 1 mM. Cells were then stimulated with test compounds for 30 minutes, after which time 5 ul of detection reagent was added and incubated for 1-7 hrs at room temperature. TR-FRET signal was detected using the Viewlux (Perkin Elmer Inc., Boston MA). EC_{50} values were determined using Graph Pad Prizm analysis (GraphPad Software, Inc). The EC_{50} values for a wide range of bile acids generated from this assay were in agreement with the values published in the scientific literature. None of the compounds induced cAMP in HEK-293 cells that were transfected with an empty vector alone, confirming a TGR5 mechanism of action for cAMP production. The symbol (+) denotes an EC_{50} value of ≤ 10 μM while the symbol (-) denotes an EC_{50} value of >10 μM (see Table 1).

Glucagon-like Peptide-1 (GLP-1) Secretion Assay:

[0243] NCI-H716 cells, human enteroendocrine (ATCC# CCL-251) have been shown to express TGR5 (Maruyama T. et al, BBRC 298, 714-719, 2002) and to secrete GLP-1 in response to nutrients such as fatty acids and meat hydolysate (Reimer R. *et al*, *Endocrinology* 142: 4522-4528). Cells were cultured and maintained in RPMI1640 (Invitrogen, Carlsbad, CA) supplemented with 10% FBS, 1% penicillin/streptomycin and 1% sodium pyruvate. Two days before GLP-1 secretion assays, $1x10^5$ cells were seeded in 96 well culture plates coated with Matrigel (BD Biosciences, Bedford, MA). On the day of experiment, the culture medium was removed and the cells were washed

twice with KRB buffer (116 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl2, 25 mM NaHCO3, 1.2 mM K2HPO4, 1.2 mM MgCl2, 25 mM HEPES, 0.2% BSA, pH 7.3). Test compounds (or DMSO control, 0.1 % final concentration) were added to the cells in the same buffer and were incubated at 37C for 2 hrs. Supernatants were then collected, centrifuged at 2000 rpm for 5 min to remove cell debris and were used to measure GLP-1 by ELISA (Linco Research, Inc., St. Charles, MO). This kit measures the biologically active GLP-1 (7-36 amide and 7-37). All compounds were tested at 10 μM. The activity of the compounds is expressed as (+ or -) based of the ability of the compound to induce a statistically significant GLP-1 secretion above the DMSO vehicle control at 10 μM. The authors theorize, although they do not wish to be held to this theory, that the compounds which score positive in this assay are more likely to induce GLP-1 secretion *in vivo*, and therefore possess a better therapeutic profile for the claimed indications (see Table 1).

Table 1 – Biological Acitivity

Example No.	**cAMP Production in 293-TGR5 Cells EC_{50}: (+): ≤ 10 μM; (-): > 10 μM**	**GLP-1 Secretion: (+): statistically significant above the DMSO control at 10 μM; (-): not statistically significant above the DMSO control at 10 μM; NT = not tested**
1	+	NT
2	+	NT
3	-	NT
4	-	NT
5	-	NT
6	+	NT
7	-	NT

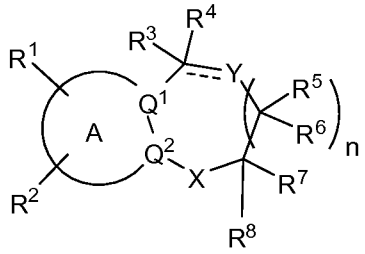
8	-	NT
9	-	NT
10	-	NT
11	-	NT
12	-	NT
13	+	NT

[0244] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A method of treatment of a TGR5-mediated disease comprising the administration, to a patient in need thereof, of a therapeutically effective amount of a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

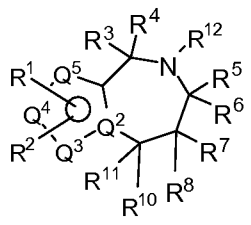
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

2. The method as recited in Claim 1, wherein said compound has structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

Q^2 is selected from the group consisting of N and C;

Q^3, Q^4, and Q^5 are independently selected from the group consisting of N and C, any of which may be optionally substituted by a substituent selected from the group consisting of hydrogen, R^1, and R^2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

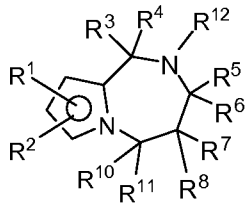
R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

3. The method as recited in Claim 2, wherein said compound has structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

4. The method as recited in Claim 3, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

5. The method as recited in Claim 4, wherein:

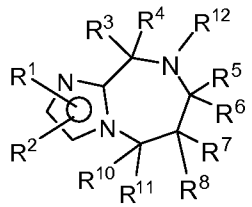
R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl;

R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

6. The method as recited in Claim 5, wherein R^3 is 2-methylphenyl.

7. The method as recited in Claim 2, wherein said compound has structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

8. The method as recited in Claim 7, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

9. The method as recited in Claim 8, wherein:

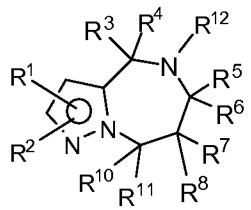
R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl;

R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

10. The method as recited in Claim 9, wherein R^3 is 2-methylphenyl.

11. The method as recited in Claim 2, wherein said compound has structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

12. The method as recited in Claim 11, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

13. The method as recited in Claim 12, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl;

R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

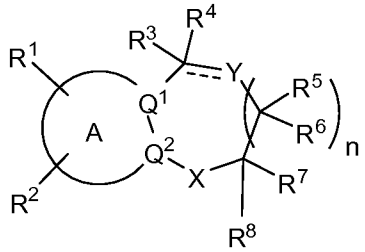
14. The method as recited in Claim 13, wherein R^3 is 2-methylphenyl.
15. The method as recited in Claim 1 wherein said compound is selected from the group consisting of Examples 1 to 13.
16. The method as recited in Claim 1 wherein said disease is a metabolic disease.
17. The method as recited in Claim 16 wherein said disease is selected from the group consisting of inadequate glucose tolerance, insulin resistance, type I diabetes, and type II diabetes.
18. The method as recited in Claim 16 further comprising the administration of another therapeutic agent.
19. The method as recited in Claim 18, wherein said agent is selected from the group consisting of insulin, metformin, Glipizide, glyburide, Amaryl, gliclazide, meglitinides, nateglinide, repaglinide, pramlintide, PTP-112, SB-517955, SB-4195052, SB-216763, NN-57-05441, NN-57-05445, GW-0791, AGN-$^{19}4^{20}4$, T-1095, BAY R3401, acarbose, miglitol, voglibose, Exendin-4, DPP728, LAF237, vildagliptin , BMS477118, PT-100, GSK-823093, PSN-9301, T-6666, SYR-322, SYR-619, Liraglutide, CJC-1134-PC, naliglutide, MK-0431, saxagliptin, GSK23A, pioglitazone, rosiglitazone, AVE2268, GW869682, GSK189075, APD668, PSN-119-1, PSN-821, rosuvastatin, atrovastatin, simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, fenofibrate, benzafibrate, clofibrate, gemfibrozil, Ezetimibe, eflucimibe, CP-529414, CETi-1, JTT-705, cholestyramine, colestipol, niacin, implitapide, (*R*)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}2,3-dihydro-1*H*-indole-2-carboxylic acid, and GI-262570.

20. The method as recited in Claim 1 wherein said disease is associated with perturbed bile acid metabolism.
21. The method as recited in Claim 20 further comprising the administration of another therapeutic agent.
22. The method as recited in Claim 1 wherein said disease is an inflammatory disease.
23. The method as recited in Claim 22 wherein said disease is selected from the group consisting of rheumatoid arthritis, ulcerative colitis, and inflammatory bowel disease.
24. The method as recited in Claim 22 further comprising the administration of another therapeutic agent.
25. The method as recited in Claim 24, wherein said agent is selected from the group consisting of betamethasone dipropionate, betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream, guaifenesin, amitryptiline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin, clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil, acetaminophen, infliximab, etanerecept, infliximab, and capsaicin.
26. The method as recited in Claim 1 wherein said disease is obesity.
27. The method as recited in Claim 26 wherein said method has achieves an effect selected from the group consisting of decreasing body weight and controlling weight gain.

28. The method as recited in Claim 26 further comprising the administration of another therapeutic agent.
29. The method as recited in Claim 28, wherein said agent is selected from the group consisting of sibutramine, bromocriptine, Orlistat, rimonabant, Axokine, and bupropion.
30. A method for achieving an effect selected from the group consisting of:

improving glucose tolerance, decreasing insulin resistance, decreasing body weight, controlling weight gain, modulation of type I diabetes, modulation of type II diabetes, modulation of perturbed bile acid metabolism, modulation of rheumatoid arthritis, modulation of ulcerative colitis, and modulation of inflammatory bowel disease in a patient;

comprising the administration of a therapeutically effective amount of a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of

which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

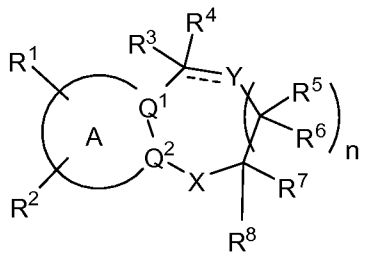
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

31. A method of modulation of TGR5 comprising contacting TGR5 with a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

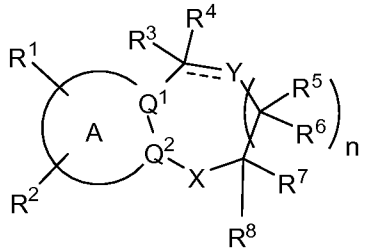
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier together with a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of

which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

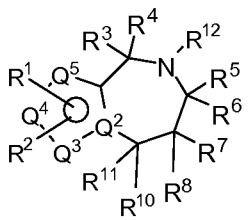
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

33. The pharmaceutical composition as recited in Claim 32, wherein said compound has structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

Q^2 is selected from the group consisting of N and C;

Q^3, Q^4, and Q^5 are independently selected from the group consisting of N and C, any of which may be optionally substituted by a substituent selected from the group consisting of hydrogen, R^1, and R^2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

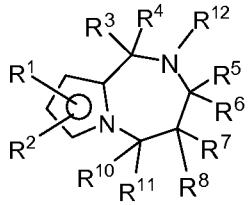
R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

34. The pharmaceutical composition as recited in Claim 33, wherein said compound has structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

35. The pharmaceutical composition as recited in Claim 34, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of

lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

36. The pharmaceutical composition as recited in Claim 35, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl;

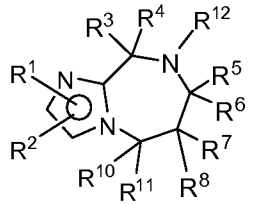
R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

37. The pharmaceutical composition as recited in Claim 36, wherein R^3 is 2-methylphenyl.

38. The pharmaceutical composition as recited in Claim 33, wherein said compound has structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

39. The pharmaceutical composition as recited in Claim 38, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

40. The pharmaceutical composition as recited in Claim 39, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl;

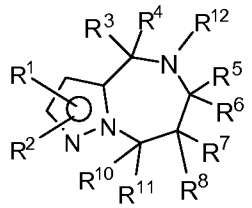
R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

41. The pharmaceutical composition as recited in Claim 40, wherein R^3 is 2-methylphenyl.

42. The pharmaceutical composition as recited in Claim 33, wherein said compound has structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

43. The pharmaceutical composition as recited in Claim 42, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

44. The pharmaceutical composition as recited in Claim 43, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl;

R^3 is phenyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

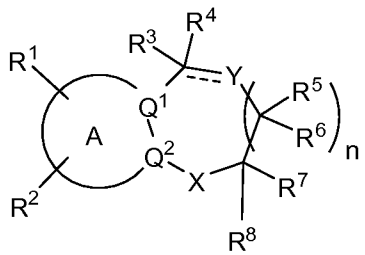
R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

45. The pharmaceutical composition as recited in Claim 44, wherein R^3 is 2-methylphenyl.

46. A pharmaceutical composition comprising a pharmaceutically acceptable carrier together with a compound selected from the group consisting of Examples 1 to 13.

47. A compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

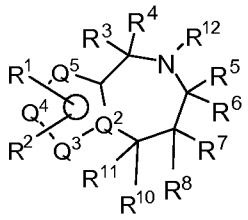
R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

48. The compound as recited in Claim 47, having structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

Q^2 is selected from the group consisting of N and C;

Q^3, Q^4, and Q^5 are independently selected from the group consisting of N and C, any of which may be optionally substituted by a substituent selected from the group consisting of hydrogen, R^1, and R^2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

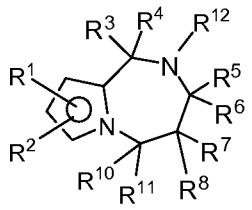
R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

49. The compound as recited in Claim 48 having structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

50. The compound as recited in Claim 49, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of

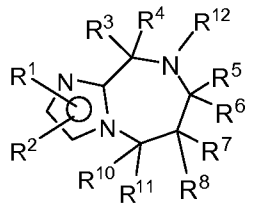
lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

51. The compound as recited in Claim 50, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

52. The compound as recited in Claim 48 having structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

53. The compound as recited in Claim 52, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

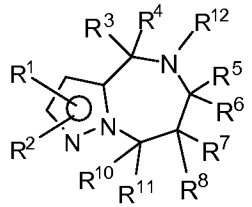
R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

54. The compound as recited in Claim 53, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

55. The compound as recited in Claim 48 having structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is 2-methylphenyl;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, and cycloalkyl, any of which may be optionally substituted;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, lower alkyl, halogen, and lower perhaloalkyl, any of which may be optionally substituted; and

R^{12} is selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted.

56. The compound as recited in Claim 55, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl;

R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} are hydrogen; and

R^{12} is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, heterocycloalkylcarbonyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

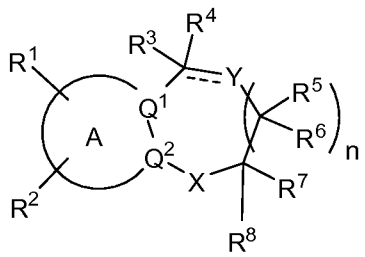
57. The compound as recited in Claim 56, wherein:

R^1 and R^2 are selected from the group consisting of hydrogen and lower alkyl; and

R^{12} is benzoyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower perhaloalkyl, halogen, lower alkoxy, lower thioalkyl, cyano, and hydroxyl.

58. A compound selected from the group consisting of Examples 1 to 13.

59. A compound for use as a medicament having structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

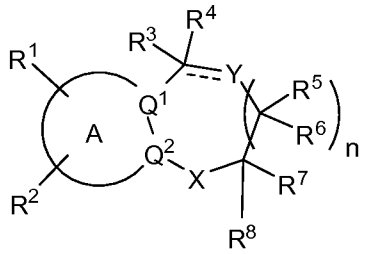
R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of

which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

60. A compound for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the modulation of TGR5 having structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

A is a five- or six-membered monocyclic heterocycloalkyl ring;

X is selected from the group consisting of $N(R^9)$, $C(R^{10})(R^{11})$, O and S, and;

Y is selected from the group consisting of $N(R^{12})$ and $C(R^{13})(R^{14})$;

Q^1 and Q^2 are independently selected from the group consisting of N and $C(R^{15})$;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of null, acyl, alkyl, alkenyl, alkynyl, alkoxy, amido, amino, aryl, aryloxy, carbamate, carboxy, cyano, cycloalkyl, halogen, heteroalkyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxyl, mercaptyl, nitro, perhaloalkoxy, perhaloalkyl, and sulfonamide, any of which may be optionally substituted; or R^1 and R^2 together may form aryl, cycloalkyl, or heterocycloalkyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl,any of which may be optionally substituted;

R^4 is selected from the group consisting of a bond, hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, any of which may be optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^7 and R^8 are taken together to form oxo (=O);

R^9 is selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, alkynyl, C-amido, carboxyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{10} and R^{11} may be taken together to form a cycloalkyl or heterocycloalkyl ring;

R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of a bond, hydrogen, acyl, C-amido, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, and sulfonyl, any of which may be optionally substituted; and

R^{15} is selected from the group consisting of a bond, hydrogen, and lower alkyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085267

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5517 C07D487/04 A61P3/00

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)
A61K C07D A61P

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, WPI Data, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 960 770 A (MORIWAKI MINORU [JP] ET AL) 2 October 1990 (1990-10-02) abstract column 6, line 60 - line 63 column 15; example 7 column 18; example 11	1,16,22, 30-32, 47,59,60
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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 :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 2008	02/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Garabatos-Perera, J

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	DATABASE REGISTRY chemical library supplier 20 July 2005 (2005-07-20), XP002476067 retrieved from STN accession no. 856140-17-5 abstract	1-60
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Y	DATABASE REGIST chemical library supplier 4 June 2005 (2005-06-04), XP002476069 retrieved from STN accession no. 853702-56-4 abstract	1-60
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Information on patent family members

International application No
PCT/US2007/085267

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