TREATING PAIN, DIABETES, AND DISORDERS OF LIPID METABOLISM

BACKGROUND

Treatment of chronic pain, particularly inflammatory and neuropathic pain, is an area of high unmet medical need. Neuopathic pain is nerve injury resulting in hyperexcitability of neurons involved in pain sensation. T-currents are present in neurons of pain pathways. T-type calcium channel blockers are effective in preclinical models of neuropathic pain.

Type II diabetes, also known as non-insulin dependent diabetes mellitus, is a progressive disease characterized by impaired glucose metabolism resulting in elevated blood glucose levels. Patients with type II diabetes exhibit impaired pancreatic beta-cell function resulting in failure of the pancreatic beta-cells to secrete an appropriate amount of insulin in response to a hyperglycemic signal,. and resistance to the action of insulin at its target tissues (insulin resistance).

Current treatments of type II diabetes aim to reverse insulin resistance, control intestinal glucose absorption, normalise hepatic glucose production, and improve beta-cell glucose sensing and insulin secretion. The sulfonylurea class of oral antihyperglycemic agents promote insulin secretion from pancreatic beta-islet cells, but have the potential to cause hypoglycemia as their action is independent of glucose levels. Antihyperglycemic agents include: insulin sensitizers that reduce hepatic glucose production by inhibiting gluconeogenesis; α-glucosidase inhibitors that inhibit breakdown of complex carbohydrates thus delaying glucose absorption and dampening postprandial glucose and insulin peaks; and thiazolidinediones that improve the action of insulin and reduce insulin resistance. Over time approximately one-half of type II diabetes patients lose their response to these agents. Because of the shortcomings of current treatments, new treatments for type II diabetes are highly desirable.

GPR119 is a constitutively active G-protein coupled receptor expressed predominantly in pancreatic beta-islet cells. Activation of GPR119 by an agonist increases insulin release from pancreatic beta-islet cells in a glucose dependent manner. Thus an agonist of GPR119 offers the potential to normalize blood glucose

levels in a type II diabetic patient in response to post-prandial blood glucose elevation, but would not be expected to stimulate insulin release in the pre-prandial or fasted state.

WO 2004/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic agent.

Niemann-Pick C1-like (NPC1L1) has been identified as a critical mediator of cholesterol absorption. It has been determined that the cholestrol absorption inhibitor ezetimibe targets NPC1L1.

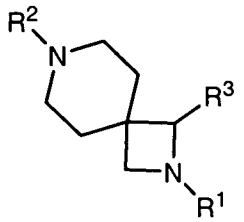
The treatment of disorders of lipid metabolism, diabetes, vascular conditions, demyelination and nonalcoholic fatty liver disease with Spirocyclic Azetidinone Derivatives has been disclosed. Spirocyclic Azetidinone Derivatives that inhibit cholesterol absorption in the small intestine are well known in the art and are described, for example, in US RE 37,721; US 5,631,356; US 5,767,115; US 5,846,966; US 5,698,548; US 5,633,246; US 5,656,624; US 5,624,920; US 5,688,787; US 5,756,470; US Publication No. 2002/0137689; WO 02/066464; WO 95/08522 and WO96/19450. Each of the aforementioned publications is incorporated by reference. The art indicates that these compounds are useful in treating, for example, atherosclerotic coronary disease, either by administrating these compounds alone or with a second compound such as a cholesterol biosynthesis inhibitor.

WO 2005/000217 describes combination therapies for the treatment of dyslipidemia comprising the administration of a combination of an anti-obesity agent and an anti-dyslipidemic agent. WO 2004/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic agent. US 2004/0122033 describes combination therapies for the treatment of obesity comprising the administration of a combination of an appetite suppressant and/or metabolic rate enhancers and/or nutrient absorption inhibitors. US 2004/0229844 describes combination therapies for treating atherosclerosis comprising the administration of a combination of nicotinic acid or another nicotinic acid receptor agonist and a DP receptor antagonist. Also known is a method for treating nonalcoholic fatty liver disease in a mammal by administering an effective amount of therapeutic composition comprising at least one cholesterol lowering agent and/or at least one H_3 receptor antagonist/inverse agonist.

A welcome contribution to the art would be methods for the treatment of pain, and methods for the treatment of diabetes (e.g., type II diabetes). This invention provides such a contribution.

SUMMARY OF THE INVENTION

The present invention claims a method of treating a disease or condition, wherein said disease or condition is mediated by T-calcium channels (e.g., pain) or by GPR119 receptors (e.g., diabetes, such as type II diabetes) or by an NPC1L1 receptor (e.g., inhibition of cholesterol absorption) comprising administering to a patient in need of such treatment at least one compound of the formula:



(I)

wherein said compound is selected from the group consisting of the compounds defined by Tables 1, 2, 3a, 3b, 3c, 3d and 4a, as described below. Table 1 provides the definitions of R^1 and assigns each moiety a number that is used in Tables 3a, 3b, 3c, 3d and 4a to define the compounds represented by the structure assigned to Tables 3a, 3b, 3c, 3d and 4a. Table 2 provides the definitions of R^2 and assigns each moiety a number that is used in Tables 3a, 3b, 3c, and 3d to define the compounds represented by the structure assigned to Tables 3a, 3b, 3c, and 3d.

The compounds useful in this invention are defined by an "X" in Tables 3a, 3b, 3c, and 3d, and are defined by the compounds in Table 4a. Thus, (1) the compounds defined by the formulas assigned to Tables 3a, 3b, 3c, 3d, having the R^1 and R^2 definitions indicated by an "X" in the box formed by the intersection of the R^2 column and the R^1 row are within the scope of this invention (i.e., are useful in the methods of this invention), boxes without an "X" define compounds that are not within the scope of the invention, and (2) the compounds defined in Table 4a are useful in the methods of this invention. The numbers in the first column in Tables 3a, 3b, 3c, and 3d represent the R^2 groups defined in Table 2. The numbers in the top row of Tables 3a, 3b, 3c, and 3d, as well as the numbers in Table 4a, represent the R^1 groups defined in Table 1.

The compounds used in the present invention are T-type calcium channel blockers. The T-calcium channel blocker compounds of formula I are useful in the

treatment of pain (such as, for example, inflammatory pain, chronic pain and neuropathic pain).

Thus, in another aspect, the present invention relates to a method of treating pain (such as for example, inflammatory pain, chronic or neuropathic pain) comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I.

In another aspect, the present invention relates to a method of treating pain (such as for example, inflammatory pain, chronic pain or neuropathic pain) comprising administering to a patient in need of such treatment an effective amount of a compound of formula I.

In another aspect, the present invention relates to a method of treating chronic pain comprising administering to a patient in need of such treatment an effective amount at least one (e.g., one) compound of formula I.

More particularly, in another aspect, the present invention relates to a method of treating inflammatory pain comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I.

Also, more particularly, in another aspect, the present invention relates to a method of treating neuropathic pain comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I.

In another aspect, the present invention relates to a method of treating chronic pain comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I.

More particularly, in another aspect, the present invention relates to a method of treating inflammatory pain comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I.

Also, more particularly, in another aspect, the present invention relates to a method of treating neuropathic pain comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I.

In another aspect, the present invention relates to a method of treating pain (such as for example, inflammatory pain, chronic pain or neuropathic pain) comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I selected from the group consisting of the compounds in Table 5.

In another aspect, the present invention relates to a method of treating pain (such as for example, inflammatory pain, chronic pain or neuropathic pain) comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I selected from the group consisting of the compounds in Table 7.

In another aspect, the present invention relates to a method of blocking T-calcium channels comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) compound of formula I.

Thus, in another aspect, the present invention relates to a method of treating neuropathic pain comprising the administration of an effective amount of at least one (e.g.,one) T-type calcium channel blocker of formula I to a patient in need of such treatment.

Compounds of formula I are agonists of GPR119. Compounds of formula I that are agonists of GPR119 are useful for the treatment, for example, of diabetes (e.g., type II diabetes).

Thus, in another aspect, the invention relates to a method of treating a disease mediated by a GPR 119 receptor (such as diabetes, such as type II diabetes) comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I.

In another aspect, the invention relates to a method of treating a disease mediated by a GPR 119 receptor (such as diabetes, such as type II diabetes) comprising administering to a patient in need of such treatment an effective amount of a compound of formula I.

In another aspect, the present invention relates to a method of treating a disease mediated by a GPR 119 receptor (such as diabetes, such as type II diabetes) comprising administering to a patient in need of such treatment an effective amount of at least one compound are selected from the group consisting of the compounds in Table 6.

In another aspect, the present invention relates to a method of treating a disease mediated by a GPR 119 receptor (such as diabetes, such as type II diabetes) comprising administering to a patient in need of such treatment an effective amount of at least one compound are selected from the group consisting of the compounds in Table 8.

In another aspect, the invention relates to the treatment of diabetes comprising administering to a patient in need of such treatment an effective amount of at least one (e.g., one) GPR119 agonist of formula I to a patient in need of such treatment.

The present invention also relates to the method of treating pain comprising administering to a patient in need of such treatment an effective amount of a combination of at least one compound of formula I and at least one additional agent for treating pain.

The invention further relates to the method of treating chronic pain comprising administering to a patient in need of such treatment an effective amount of a combination of at least one compound of formula I and at least one additional agent for treating chronic pain.

The invention also relates to the method of treating inflammatory pain comprising administering to a patient in need of such treatment an effective amount of a combination of at least one compound of formula I and at least one additional agent for treating inflammatory pain.

The invention also relates to the method of treating neuropathic pain comprising administering to a patient in need of such treatment an effective amount of a combination of at least one compound of formula I and at least one additional agent for treating neuropathic pain.

The present invention also relates to the method of treating diabetes (e.g., type II diabetes) comprising administering to a patient in need of such treatment an effective amount of a combination of at least one compound of formula I and at least one additional agent for treating diabetes (e.g., type II diabetes).

In particular, the invention relates to the method of treating diabetes (e.g., type II diabetes) comprising administering to a patient in need of such treatment an effective amount of a combination of at least one compound of formula I and at least one additional agent for treating diabetes.

The present invention also relates to a method of treating a disorder of lipid metabolism comprising administering to a patient in need of such treatment an effective amount of a combination of at least one compound of formula I.

The present invention also relates to a method of inhibiting the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I.

The present invention also relates to a method of inhibiting cholesterol absorption comprising administering to a patient in need of such treatment an effective amount of at least one NPC1L1 antagonist compound of formula I.

The present invention also relates to a method of inhibiting the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one additional agent useful for treating a disorder of lipid metabolism (such as, at least one additional agent useful in lowering cholesterol).

The present invention also relates to a method of inhibiting cholesterol absorption comprising administering to a patient in need of such treatment an effective amount of at least one NPC1L1 antagonist compound of formula I in combination with an effective amount of at least one additional agent useful for treating a disorder of lipid metabolism (such as at least one additional agent useful in lowering cholesterol).

The present invention also relates to a method for the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one inhibitor of HMG-CoA reductase (e.g., statins, such as, for example, simvastatin, atorvastatin calcium, and rosuvastatin calcium).

The present invention also relates to a method for the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one nicotinic acid receptor agonist (e.g., nicotinic acid).

The present invention also relates to a method for the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one inhibitor of CETP (e.g., torcetrapib).

The present invention also relates to a method for the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one NPC1L1 antagonist (such as, for example, ezetimibe, such as the Zetia® brand of ezetimibe).

The present invention also relates to a method for the inhibition of the absorption of cholesterol comprising administering to a patient in need of such

treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one inhibitor of HMG-CoA reductase (e.g., statins, such as, for example, simvastatin, atorvastatin calcium, and rosuvastatin calcium), and in combination with an effective amount of at least one NPC1L1 antagonist (such as, for example, ezetimibe, such as the Zetia® brand of ezetimibe). An example of a medicament already comprising a combination of a HMG-CoA reductase and a NPC1L1 antagonist that can be used in this embodiment is the Vytorin® brand of the combination of ezetimibe and simvastatin.

The present invention also relates to a kit comprising in a single package at least one compound of formula I in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising at least one additional therapeutic agent (such as, for example, at least one of the addition agents useful in the treatment of pain, or at least one additional agent useful in the treatment of lipid disorders (such as at least one additional agent useful in lowering cholesterol), or at least one additional agent for treating diabetes).

DETAILED DESCRIPTION

Current chronic pain therapies provide only partial relief in responsive patients and are either not tolerated or ineffective in others. Chronic pain may arise as a consequence of tissue inflammation, viral infection (HIV, Herpes zoster) direct tissue injury or trauma, as a result of chemotherapy (e.g. taxol, vincristine), lesions of the central nervous system (e.g. stroke, MS) or as a consequence of diabetes. When chronic pain is associated with somatic or visceral tissue injury, symptoms usually include severe sensory disturbances characterized by spontaneous pain (often described as stabbing, burning, electric-shock-like or throbbing), hyperalgesia (exaggerated responsiveness to painful stimuli) and allodynia (perception of non noxious stimuli as painful). Prevalent symptoms in human patients include cold hyperalgesia, tactile allodynia and less commonly, heat hyperalgesia. Symptoms may present in isolation or in combination and there is often appreciable variation in the symptomatology associated with different disease states and typically between patients presenting with the same condition. In cases of somatic or visceral tissue injury/diseases, these distorted sensory perceptions have been linked to inappropriate activity (pathological hyperexcitability) in the peripheral nerves innervating the affected

area. Neuronal hyperexcitability may arise as a result of altered ion channel function or activity.

Chronic pain is a true disease. It is believed to be a result, at least in part, of the plasticity at synapses in nociceptive processing centers, a phenomenon referred to as "central sensitization" which consists of increased excitability of spinal cord dorsal horn neurons. Maintenance of central sensitization is believed to require sustained peripheral neuronal activity (hyperexcitability) in sensory afferent nerves and such activity may be generated as a result of ectopic foci. Large T-type calcium currents can be found in sensory afferent neurons of the dorsal root ganglia (DRG). T-type calcium channels have been implicated as a causal factor in establishing such abnormal hyperexcitability, due to their known ability to function as neuronal pacemakers. Pharmacological and antisense oligonucleotide evidence supports a key role for DRG T-type calcium channels preclinical models of chronic pain.

T-type calcium channels are voltage-gated channels that can be opened with relatively small depolarizations from the resting potential of excitable cells. There are three distinct genes for T-type calcium currents that encode for $Ca_V3.1$, $Ca_V3.2$ and $Ca_V3.3$. The individual subtypes have unique patterns of distribution and are expressed in peripheral and central portions of pain pathways. T-type calcium channels are found in small and medium sized DRG neurons ($Ca_V3.2$) and regions of the CNS involved in pain processing including the dorsal horn of the spinal cord an the thalamus (Talley et al, *J Neurosci*, 1999, 19:1895-1911). T-type calcium currents have been shown to play a role in neuronal burst firing via low-threshold calcium spikes that permit rapid burst of neuronal action potentials (Suzuki and Rogwoski, Proc Natl Acad Sci USA, 1989, 86:7228-7232; White et al., *Proc Natl Acad Sci USA*, 1989, 86:6802-6806).

Inhibition of T-type calcium channel function *in vivo* through either the use of pharmacological blockers or antisense oligonucleotide mediated knockdown strongly implicate T-type channels in normal and pathological pain processing. Mibefradil and/or ethosuximide are selective for T-type calcium channel and have been shown to be effective in a number of preclinical pain models including: acute thermal and mechanical pain, phase I and II of the formalin model, the rat spinal nerve ligation model, capsaicin-induced mechanical hyperalgesia, rat tail flick, paclitaxil- and vincristine-induced chemoneuropathy (Barton et al., *Eur J Pharmacol*, 2005, 521:79–

8; Dogrul et al *Pain,* 2003, 105:159:168; Flatters and Bennett, *Pain*, 2004, 109:150-161; Todorovic et al., *Brain Res*, 2002, 951:336-340).

Pain relief in response to ethosuximide could be due to either central or peripheral actions. However efficacy in response to mibefradil can be attributed to peripheral effects for two reasons. First systemically administered mibefradil does not enter the brain. In addition intrathecal administration of mibefradil is ineffective (Dogrul et al *Pain,* 2003, 105:159:168). Further evidence supporting efficacy from block of peripheral T-type channels comes from studies with antisense oligonucleotide directed against on type of T-type channel, $Ca_V3.2$. Intrathecal injection of hCaV3.2 specific oligonucleotides decreased T-type calcium currents in DRG neurons and produced antinociceptive, anti-hyperalgesic and anti-allodynic effects. In these studies the uptake of oligonucleotide and the antisense mediated knockdown of T-type currents occurred in DRG neurons close to the site of injection but not in spinal cord (Bourinet et al., *EMBO J*, 2005 24:315-324).

The compounds of formula I of this invention are T-type calcium channel blockers. Accordingly, the present compounds are useful in the treatment or prevention of conditions that are treatable or preventable by administering T-type calcium channel blockers. Such conditions include the treatment or prevention of neuropathic pain.

Neuropathic pain as used herein refers to an abnormal state of pain sensation, in which a reduction of pain threshold and the like are continued, due to functional abnormalities accompanying damage or degeneration of a nerve, plexus or perineural soft tissue, which is caused by wound (e.g., lacerations, contusions, nerve avulsion injuries, amputation of a limb), compression (carpal tunnel syndrome, trigeminal neuralgia, tumor activity), infection, cancer, ischemia and the like, or metabolic disorders such as diabetes mellitus and the like. Neuropathic pain includes pain caused by either central or peripheral nerve damage. It also includes the pain caused by either mononeuropathy or polyneuropathy. In some embodiments, the neuropathic pain is induced by diabetes.

Other examples of neuropathic pain treatable or preventable by the present compounds include, but are not limited to, allodynia (a pain sensation induced by mechanical or thermal stimulus that does not normally provoke pain), hyperalgesia (an excessive response to a stimulus that is normally painful), hyperesthesia (an excessive response to a contact stimulus), diabetic polyneuropathy, entrapment

neuropathy, cancer pain, central pain, labor pain, myocardial infarction pain, post-stroke pain, pancreatic pain, colic pain, muscle pain, post-operative pain, post-stroke pain, pain associated with Parkinson's disease, pain associated with intensive care, pain associated with a periodontal disease (including gingivitis and periodontitis), menstrual pain, migraine pain, persistent headaches (e.g., cluster headache or chronic tension headache), persistent pain states (e.g., fibromyalgia or myofascial pain), trigeminal neuralgia, postherpetic neuralgia, bursitis, pain associated with AIDS, pain associated with multiple sclerosis, pain due to spinal trauma and/or degeneration, burn pain, referred pain, enhanced memory of pain and neuronal mechanisms involved in coping with pain. Inflammatory pain may arise as a result of soft tissue injury including that involving the musculature (myositis) and viscera (colitis and inflammatory bowel disease, pancreatitis, cystitis, ileitis, Crohn's disease), nerves (neuritis, radiculopathies, radioculogangionitis), arthritic conditions (e.g. rheumatoid disease and related conditions such as ankylosing spondylitis), joint disease (including osteoarthritis). The compounds of the present invention are particularly useful for treating or preventing allodynia and hyperalgesia.

Additional agents for treating neuropathic pain include non-opioid analgesics, opioid analgesics, antimigraine agents, Cox-II inhibitors, antiemetics, β- adrenergic blockers, anticonvulsants, antidepressants, other Ca^{2+}-channel blockers, sodium channel blockers, anticancer agents, agents for treating or preventing UI, agents for treating hypertension, agents for treating or preventing angina pectoris, agents for treating atrial fibrillation, agents for treating insomnia, agents for treating renal failure, agents for treating Alzheimer's disease, agents for treating or preventing IBD, agents for treating or preventing IBS, agents for treating Parkinson's disease and parkinsonism, agents for treating anxiety, agents for treating epilepsy, agents for treating a stroke, agents for treating psychosis, agents for treating Huntington's chorea, agents for treating ALS, agents for treating vomiting, agents for treating dyskinesia, and agents for treating depression.

Preferred additional agents for treating neuropathic pain include those selected from the group consisting of: non-opioid analgesics and opioid analgesics.

Additional agents for treating inflammatory pain include corticosteroids, non-sterodial anti-imflammatory agents, COX-I and COX-II inhibitors, agents useful for treating inflammatory bowel disease and agents useful for treating rheumatoid arthritis.

Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. There are two major forms of diabetes: Type I diabetes (also referred to as insulin-dependent diabetes or IDDM) and Type II diabetes (also referred to as noninsulin dependent diabetes or NIDDM). Compounds of formula II are useful in treating Type II diabetes.

Type I diabetes is the result of an absolute deficiency of insulin, the hormone that regulates glucose utilization. This insulin deficiency is usually characterized by β cell destruction in the pancreas, which usually leads to absolute insulin deficiency. Type I diabetes has two forms: Immune-Mediated Diabetes Mellitus, which results from a cellular mediated autoimmune destruction of the β cells of the pancreas; and Idiopathic Diabetes Mellitus, which refers to forms of the disease that have no known etiologies.

Type II diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type II diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of insulin are present to compensate for insulin resistance and adequately control glucose, a state of impaired glucose tolerance develops. Insulin secretion may further decline over time.

Type II diabetes can be due to a resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues, such as muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type II diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

In particular, Type II diabetes can be treated by treatment with a GPR119 agonist of formula II, alone or in combination with one or more additional agents for treating diabetes.

Other therapies for the treatment of type II diabetes that can be used in combination with compounds of formula II of this invention for treating Type II diabetes include sulfonylureas, insulin sensitizers, PPAR agonists, α-glucosidase inhibitors, insulin secretagogues, hepatic glucose output lowering compounds, and insulin.

The compounds of formula I of this invention are NPC1L1 antagonists and are therefore useful for treating disorders of lipid metabolism, in particular for inhibiting absorption of cholesterol.

The compounds of formula I are useful for treating disorders of lipid metabolism. The compounds of formula I are NPC1L1 antagonists. In one embodiment, the compounds of formula I are therefore useful for treating disorders of lipid metabolism, in particular for inhibiting absorption of cholesterol. It is to be understood that when the compounds of formula I are administered for inhibiting the absorption of cholesterol in a patient, the inhibition may be partial or complete. Accordingly, in one embodiment, the absorption of cholesterol in a patient is partially inhibited. In another embodment, the absorption of cholesterol in a patient is completely inhibited.

Methods of treating disorders of lipid metabolism include treating hyperlipidemia, hypercholesterolaemia, hypertriglyceridaemia, sitosterolemia and arteriosclerotic symptoms; inhibiting absorption of cholesterol from the intestine; reducing blood plasma or serum concentrations of LDL cholesterol; reducing the concentrations of cholesterol and cholesterol ester in blood plasma or serum; reducing blood plasma or serum concentrations of C-reactive protein (CRP); reducing blood plasma or serum concentrations of triglycerides; reducing blood plasma or serum concentrations of apolipoprotein B; increasing blood plasma or serum concentrations of high density lipoprotein (HDL) cholesterol; increasing the fecal excretion of cholesterol; treating a clinical condition for which a cholesterol absorption inhibitor is indicated; reducing the incidence of cardiovascular disease-related events; reducing plasma or tissue concentration of at least one non-cholesterol sterol or 5α-stanol; treating or preventing vascular inflammation; preventing, treating or ameliorating symptoms of Alzheimer's Disease; regulating the production or level of at least one amyloid β peptide in the bloodstream and/or brain of a patient; regulating the amount of ApoE isoform 4 in the bloodstream and/or brain; preventing and/or treating obesity; and preventing or decreasing the incidence of xanthomas.

A method of treating a disorder of lipid metabolism comprises administering a cholesterol absorption inhibitor of formula I.

Additional agents for treating a disorder of lipid metabolism include inhibitors of cholesterol absorption (e.g., NPC1L1 antagonists, such as, for example, ezetimibe (such as the Zetia® brand of ezetimibe)), inhibitors of cholesterol biosynthesis, including, but not limited to HMG CoA reductase inhibitors (such as statins, such as, for example, simvastatin (such as the Zocor® brand of simvastatin), atorvastatin calcium (such as the Lipitor® brand of atorvastatin calcium), and rosuvastatin calcium (such as the Crestor® brand of rosuvastatin calcium)), inhibitors of cholesterol biosynthesis, cholesterol ester transfer protein (CETP) inhibitors (e.g., torcetrapib), bile acid sequesterants, a nicotinic acid receptor agonist such as nicotinic acid or a derivative thereof (e.g., Niacin (nicotinic acid), and the Niaspan® brand of niacin extended release tablets), peroxisome proliferator-activator receptor (PPAR) alpha agonists or activators, acylcoenzyme A:cholesterol acyltransferase (ACAT) inhibitors; obesity control medications, hypoglycemic agents, antioxidants, antihypertensive agents, ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors, probucol or derivatives thereof; low-density lipoprotein ("LDL") receptor activators; omega 3 fatty acids ("3-PUFA"); natural water soluble fibers; plant sterols, and plant stanols and/or fatty acid esters of plant stanols.

US Provisional Application 60/752710, filed December 20, 2005, and US Provisional Application 60/77048, filed March 29, 2006, disclose the use of cholesterol absorption inhibitors.

Classes of cholesterol lowering agents useful in the present methods for treating disorders of lipid metabolism include the following non-limiting classes of agents: NCP1L1 inhibitors such as ezetimibe; HMG-CoA reductase inhibitors; bile acid sequestrants; PPAR agonists or activators; ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors; nicotinic acid (niacin) and/or nicotinic acid receptor agonists; acylCoA:cholesterol *O*-acyltransferase ("ACAT") inhibitors; cholesteryl ester transfer protein ("CETP") inhibitors; probucol or derivatives thereof; low-density lipoprotein ("LDL") receptor activators; omega 3 fatty acids ("3-PUFA"); natural water soluble fibers; plant sterols, plant stanols and/or fatty acid esters of plant stanols.

Non-limiting examples of suitable cholesterol biosynthesis inhibitors useful in the present methods include competitive inhibitors of HMG-CoA reductase, the rate-

limiting step in cholesterol biosynthesis, squalene synthase inhibitors, squalene epoxidase inhibitors and mixtures thereof. Non-limiting examples of suitable HMG-CoA reductase inhibitors useful in the present methods include statins such as lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, cerivastatin, CI-981, resuvastatin, rivastatin and pitavastatin, rosuvastatin; HMG-CoA reductase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other sterol biosynthesis inhibitors such as DMP-565. Preferred HMG-CoA reductase inhibitors include lovastatin, pravastatin and simvastatin. The most preferred HMG-CoA reductase inhibitor is simvastatin.

Generally, a total daily dosage of cholesterol biosynthesis inhibitor(s) can range from about 0.1 to about 160 mg per day. In one embodiment, the dosage is from about 0.2 to about 80 mg/day, administered in a single dose or in 2-3 divided doses.

Bile acid squestrants bind bile acids in the intestine, interrupting the enterohepatic circulation of bile acids and causing an increase in the faecal excretion of steroids.

Non-limiting examples of suitable bile acid sequestrants useful in the present methods include cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

The activators or agonists of PPAR act as agonists for the peroxisome proliferator-activated receptors. Three subtypes of PPAR have been identified, and these are designated as peroxisome proliferator-activated receptor alpha (PPARα),

peroxisome proliferator-activated receptor gamma (PPARγ) and peroxisome proliferator-activated receptor delta (PPARδ). It should be noted that PPARδ is also referred to in the literature as PPARβ and as NUC1, and each of these names refers to the same receptor.

PPARα regulates the metabolism of lipids. PPARα is activated by fibrates and a number of medium and long-chain fatty acids, and it is involved in stimulating β-oxidation of fatty acids. The PPARγ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. PPARδ has been identified as being useful in increasing high density lipoprotein (HDL) levels in humans. See, e.g., WO 97/28149.

PPARα activator compounds are useful for, among other things, lowering triglycerides, moderately lowering LDL levels and increasing HDL levels. Useful examples of PPARα activators include fibrates.

Non-limiting examples of suitable fibric acid derivatives ("fibrates") useful in the present methods include clofibrate; gemfibrozil; ciprofibrate; bezafibrate; clinofibrate; binifibrate; lifibrol; fenofibrate and mixtures thereof. These compounds can be used in a variety of forms, including but not limited to acid form, salt form, racemates, enantiomers, zwitterions and tautomers.

Other examples of PPARα activators useful in the present methods include suitable fluorophenyl compounds as disclosed in U.S. No. 6,028,109 which is incorporated herein by reference; certain substituted phenylpropionic compounds as disclosed in WO 00/75103 which is incorporated herein by reference; and PPARα activator compounds as disclosed in WO 98/43081 which is incorporated herein by reference.

Non-limiting examples of suitable PPARγ activators useful in the present methods include derivatives of glitazones or thiazolidinediones, such as, troglitazone; rosiglitazone and pioglitazone. Other useful thiazolidinediones include ciglitazone, englitazone, darglitazone and BRL 49653 as disclosed in WO 98/05331 which is incorporated herein by reference; PPARγ activator compounds disclosed in WO 00/76488 which is incorporated herein by reference; and PPARγ activator compounds disclosed in U.S. Patent No. 5,994,554 which is incorporated herein by reference.

Other useful PPARγ activator compounds useful in the present methods include certain acetylphenols as disclosed in U.S. Patent No. 5,859,051 which is incorporated herein by reference; certain quinoline phenyl compounds as disclosed in

WO 99/20275 which is incorporated herein by reference; aryl compounds as disclosed by WO 99/38845 which is incorporated herein by reference; certain 1,4-disubstituted phenyl compounds as disclosed in WO 00/63161; certain aryl compounds as disclosed in WO 01/00579 which is incorporated herein by reference; benzoic acid compounds as disclosed in WO 01/12612 & WO 01/12187 which are incorporated herein by reference; and substituted 4-hydroxy-phenylalconic acid compounds as disclosed in WO 97/31907 which is incorporated herein by reference.

PPARδ compounds are useful for, among other things, lowering triglyceride levels or raising HDL levels. Non-limiting examples of PPARδ activators useful in the present methods include suitable thiazole and oxazole derivatives, such as C.A.S. Registry No. 317318-32-4, as disclosed in WO 01/00603 which is incorporated herein by reference); certain fluoro, chloro or thio phenoxy phenylacetic acids as disclosed in WO 97/28149 which is incorporated herein by reference; suitable non-ß-oxidizable fatty acid analogues as disclosed in U.S. Patent No. 5,093,365 which is incorporated herein by reference; and PPARδ compounds as disclosed in WO 99/04815 which is incorporated herein by reference.

Moreover, compounds that have multiple functionality for activating various combinations of PPARα, PPARγ and PPARδ are also useful in the present methods. Non-limiting examples include certain substituted aryl compounds as disclosed in U.S. Patent No. 6,248,781; WO 00/23416; WO 00/23415; WO 00/23425; WO 00/23445; WO 00/23451; and WO 00/63153, all of which are incorporated herein by reference, are described as being useful PPARα and/or PPARγ activator compounds. Other non-limiting examples of useful PPARα and/or PPARγ activator compounds include activator compounds as disclosed in WO 97/25042 which is incorporated herein by reference; activator compounds as disclosed in WO 00/63190 which is incorporated herein by reference; activator compounds as disclosed in WO 01/21181 which is incorporated herein by reference; biaryl-oxa(thia)zole compounds as disclosed in WO 01/16120 which is incorporated herein by reference; compounds as disclosed in WO 00/63196 and WO 00/63209 which are incorporated herein by reference; substituted 5-aryl-2,4-thiazolidinediones compounds as disclosed in U.S. Patent No. 6,008,237 which is incorporated herein by reference; arylthiazolidinedione and aryloxazolidinedione compounds as disclosed in WO 00/78312 and WO 00/78313G which are incorporated herein by reference; GW2331 or (2-(4-[difluorophenyl]-1heptylureido)ethyl]phenoxy)-2-methylbutyric compounds as disclosed in WO

98/05331 which is incorporated herein by reference; aryl compounds as disclosed in U.S. Patent No. 6,166,049 which is incorporated herein by reference; oxazole compounds as disclosed in WO 01/17994 which is incorporated herein by reference; and dithiolane compounds as disclosed in WO 01/25225 and WO 01/25226 which are incorporated herein by reference.

Other useful PPAR activator compounds useful in the present methods include substituted benzylthiazolidine-2,4-dione compounds as disclosed in WO 01/14349, WO 01/14350 and WO/01/04351 which are incorporated herein by reference; mercaptocarboxylic compounds as disclosed in WO 00/50392 which is incorporated herein by reference; ascofuranone compounds as disclosed in WO 00/53563 which is incorporated herein by reference; carboxylic compounds as disclosed in WO 99/46232 which is incorporated herein by reference; compounds as disclosed in WO 99/12534 which is incorporated herein by reference; benzene compounds as disclosed in WO 99/15520 which is incorporated herein by reference; o-anisamide compounds as disclosed in WO 01/21578 which is incorporated herein by reference; and PPAR activator compounds as disclosed in WO 01/40192 which is incorporated herein by reference.

The peroxisome proliferator-activated receptor(s) activator(s) are administered in a therapeutically effective amount to treat the specified condition, for example in a daily dose preferably ranging from about 50 to about 3000 mg per day. In one embodiment, the daily dose is from about 50 to about 2000 mg per day, administered in a single dose or in 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

In an alternative embodiment, the present invention includes the use of one or more IBAT inhibitors or ASBT inhibitors. The IBAT inhibitors can inhibit bile acid transport to reduce LDL cholesterol levels. Non-limiting examples of suitable IBAT inhibitors useful in the present methods include benzothiepines such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure such as are disclosed in PCT Patent Application WO 00/38727 which is incorporated herein by reference.

Generally, a total daily dosage of IBAT inhibitor(s) can range from about 0.01 to about 1000 mg/day. In one embodiment, the dosage is from about 0.1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses.

In another alternative embodiment, the methods of the present invention can further comprise nicotinic acid (niacin) and/or nicotinic acid receptor ("NAR") agonists as lipid lowering agents.

As used herein, "nicotinic acid receptor agonist" means any compound comprising that will act as an agonist to the nicotinic acid receptor. Compounds include those that have a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available. Examples of nicotinic acid receptor agonists useful in the present methods include niceritrol, nicofuranose and acipimox. Nicotinic acid and NAR agonists inhibit hepatic production of VLDL and its metabolite LDL and increases HDL and apo A-1 levels. An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release tablets) which are available from Kos Pharmaceuticals, Inc. (Cranbury, NJ).

Generally, a total daily dosage of nicotinic acid can range from about 500 to about 10,000 mg/day. In one embodiment, the dosage is from about 1000 to about 8000 mg/day. In another embodiment, the dosage is from about 3000 to about 6000 mg/day, administered in a single dose or in divided doses. Generally, the total daily dosage of a NAR agonist can range from about 1 to about 100 mg/day.

In another alternative embodiment, the methods of the present invention can further comprise one or more ACAT inhibitors as lipid lowering agents. ACAT inhibitors reduce LDL and VLDL levels. ACAT is an enzyme responsible for esterifying excess intracellular cholesterol and may reduce the synthesis of VLDL, which is a product of cholesterol esterification, and overproduction of apo B-100-containing lipoproteins.

Non-limiting examples of useful ACAT inhibitors useful in the present methods include avasimibe, HL-004, lecimibide and CL-277082 (*N*-(2,4-difluorophenyl)-*N*-[[4-(2,2-dimethylpropyl)phenyl]-methyl]-*N*-heptylurea). See P. Chang *et al.*, "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul;60(1); 55-93, which is incorporated by reference herein.

Generally, a total daily dosage of ACAT inhibitor(s) can range from about 0.1 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses.

In another alternative embodiment, the compositions used in the methods of the present invention can further comprise one or more Cholesteryl Ester Transfer Protein ("CETP") Inhibitors coadministered with or in combination with one of more

Spirocyclic Azetidinone Compounds. CETP is responsible for the exchange or transfer of cholesteryl ester carrying HDL and triglycerides in VLDL.

Non-limiting examples of suitable CETP inhibitors useful in the present methods are disclosed in PCT Patent Application No. WO 00/38721 and U.S. Patent No. 6,147,090, which are incorporated herein by reference. Pancreatic cholesteryl ester hydrolase (pCEH) inhibitors such as WAY-121898 also can be co-administered with or in combination with the fibric acid derivative(s) and sterol absorption inhibitor(s) discussed above.

Generally, a total daily dosage of CETP inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.5 to about 20 mg/kg body weight/day, administered in a single dose or in 2 or more divided doses.

In another alternative embodiment, the methods of the present invention can further comprise probucol or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250), which can reduce LDL and HDL levels, as cholesterol lowering agents.

Generally, a total daily dosage of probucol or derivatives thereof can range from about 10 to about 2000 mg/day. In one embodiment, the dosage is from about 500 to about 1500 mg/day, administered in a single dose or in 2-4 divided doses.

In another alternative embodiment, the methods of the present invention can further comprise one or more low-density lipoprotein (LDL) receptor activators, as lipid lowering agents. Non-limiting examples of suitable LDL-receptor activators useful in the present methods include HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity. See M. Huettinger *et al.,* "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", *Arterioscler.Thromb.* 1993; 13:1005-12.

Generally, a total daily dosage of LDL receptor activator(s) can range from about 1 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses.

In another alternative embodiment, the methods of the present invention can further comprise fish oil, which contains Omega 3 fatty acids (3-PUFA), which can reduce VLDL and triglyceride levels,as a lipid lowering agent. Generally, a total daily dosage of fish oil or Omega 3 fatty acids can range from about 1 to about 30 grams per day, administered in a single dose or in 2-4 divided doses.

In another alternative embodiment, the methods of the present invention can further comprise natural water-soluble fibers, such as psyllium, guar, oat and pectin,

which can reduce cholesterol levels. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day, administered in a single dose or in 2-4 divided doses.

In another alternative embodiment, methods of the present invention can further comprise plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels. Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant stanols can range from about 0.5 to about 20 grams per day, administered in a single dose or in 2-4 divided doses.

Thus, another embodment of the invention is directed to the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I.

Another embodment of the invention is directed to the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one additional agent for treating a disorder of lipid metabolism.

Another embodment of the invention is directed to the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one nicotinic acid receptor agonist (e.g., nicotinic acid).

Another embodment of the invention is directed to the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one inhibitor of HMG-CoA reductase (e.g., statins, such as, for example, simvastatin, atorvastatin calcium, and rosuvastatin calcium).

Another embodment of the invention is directed to the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one inhibitor of CETP (e.g., torcetrapib).

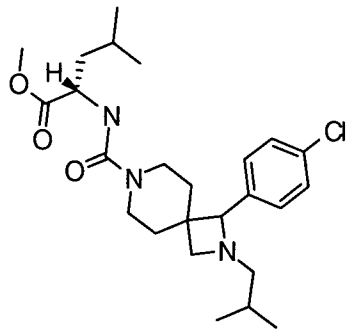
Another embodment of the invention is directed to the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination

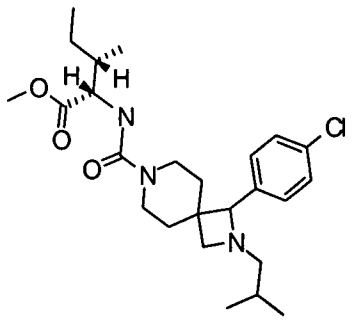
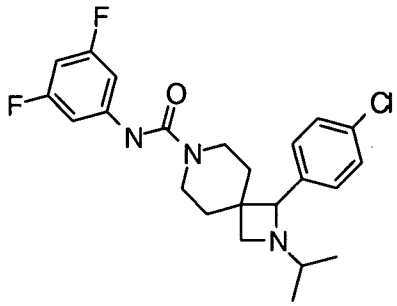
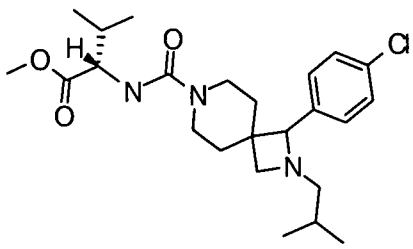
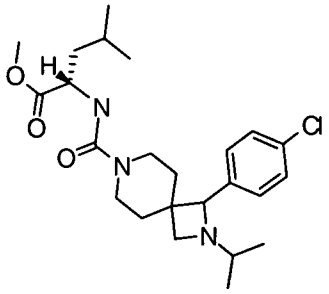
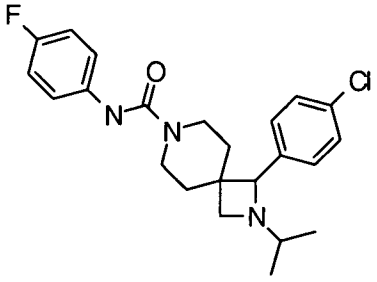
with an effective amount of at least one NPC1L1 antagonist (such as, for example, ezetimibe, such as the Zetia® brand of ezetimibe).

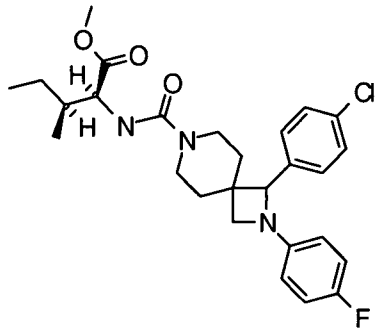
Another embodment of the invention is directed to the inhibition of the absorption of cholesterol comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I in combination with an effective amount of at least one inhibitor of HMG-CoA reductase (e.g., statins, such as, for example, simvastatin, atorvastatin calcium, and rosuvastatin calcium), and in combination with an effective amount of at least one NPC1L1 antagonist (such as, for example, ezetimibe, such as the Zetia® brand of ezetimibe). An example of a medicament already comprising a combination of a HMG-CoA reductase and a NPC1L1 antagonist that can be used in this embodiment is the Vytorin® brand of the combination of ezetimibe and simvastatin.

Preferred compounds of formula I for use as T-type calcium channel blockers are given in Table A.

Table A

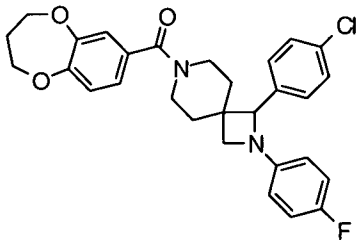
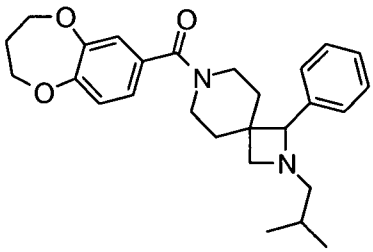
isomer	Compound
	

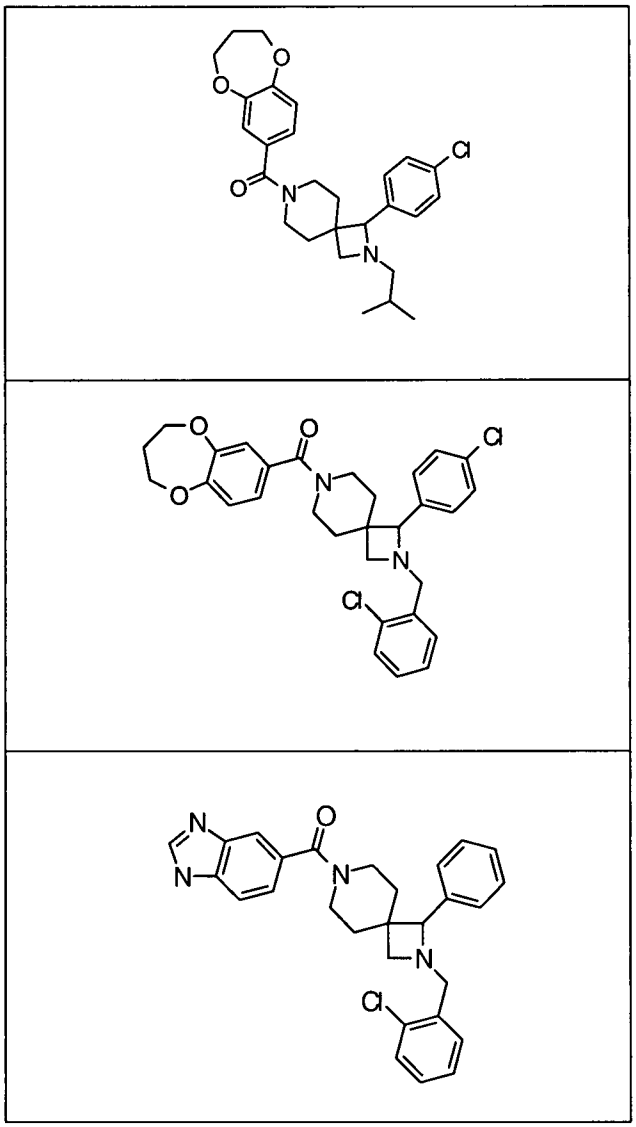
	
A	
	
	
A	

Preferred compounds of formula I for use as GPR119 agonists are those in Table B.

TABLE B

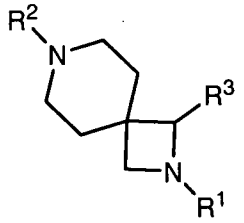
Compound





Tables 1, 2, 3a, 3b, 3c, 3d, and 4a are given below. Table 1 defines the R^1 moieties used in Tables 3a, 3b, 3c, 3d and 4a by assigning a number to the moieties which number is used in Tables 3a, 3b, 3c, 3d and 4a. Table 2 defines the R^2 moieties used in Tables 3a, 3b, 3c, and 3d by assigning a number to the moieties which number is used in Tables 3a, 3b, 3c, and 3d. With reference to the particular structure assigned to Tables 3a, 3b, 3c, and 3d, the compounds whose R^1 and R^2 moieties are defined by an "X" in the box formed by the intersection of the R^2 column and the R^1 row are included in the definition of formula I and are therefore useful in the methods of this invention (i.e., are within the scope of the invention). If there isn't an "X" in the box, the compounds having such R^1 and R^2 moieties are not within the definition of formula I (i.e., are not within the scope of the invention). The compounds defined by the structure assigned to Table 4a having the R^1 moieties defined in Table

4a are included in the definition of the compounds of formula I and are therefore useful in the methods of this invention.

Tables 1, 2, 3a, 3b, 3c, 3d, and 4a are defining compound of the formula (I):

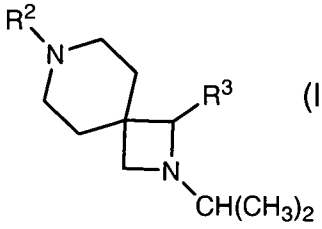


(I)

In Table 1 "#" represents number, which is the number assigned to the R^1 moiety, and is the number that is referenced in Tables 3a, 3b, 3c, 3d, and 4a.

In Table 2 "#" represents number, which is the number assigned to the R^2 moiety, and is the number that is referenced in Tables 3a, 3b, 3c, and 3d.

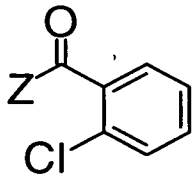
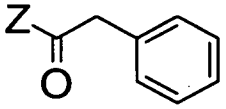
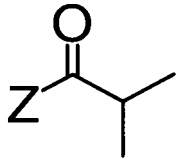
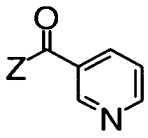
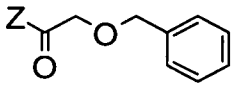
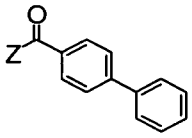
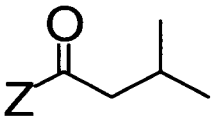
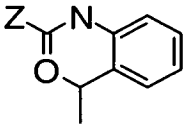
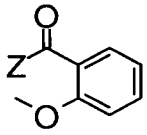
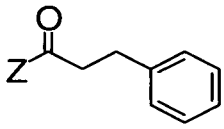
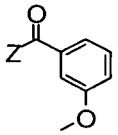
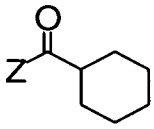
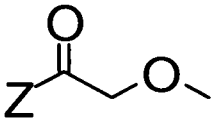
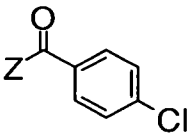
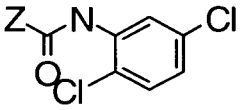
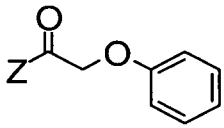
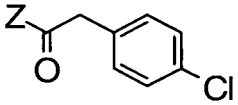
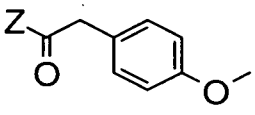
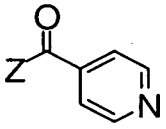
In Tables 1 and 2 "Z" represents the point of attachment to the rest of the molecule (i.e., "Z" represents where R^1 and R^2 are attached to the rest of the molecule). Thus, for example, when R^1 in Table 1 is Z-$CH(CH_3)_2$ (see moiety number 50), the compound of formula I is:



(I-1)

TABLE 1

Definition of the R^1 Moieties

R1	#	R1	#	R1	#
	2		13		22
	3		14		23
	7		15		25
	8		17		26
	9		19		27
	10		20		
	11		21		

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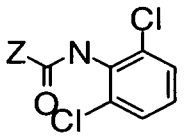
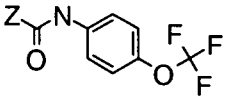
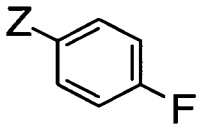
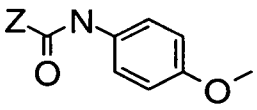
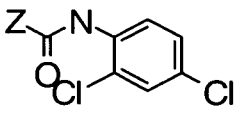
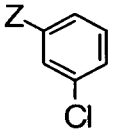
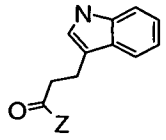
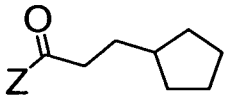
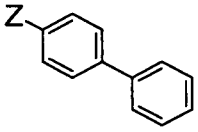
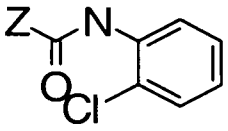
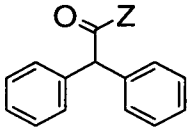
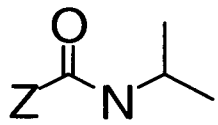
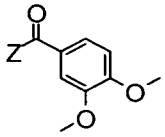
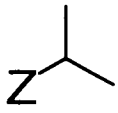
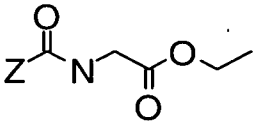
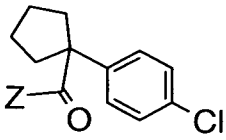
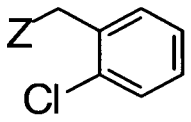
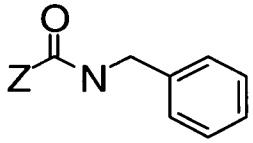
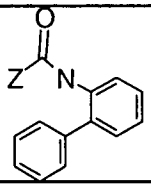
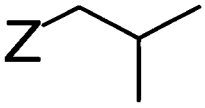
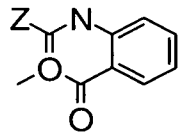
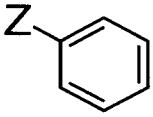
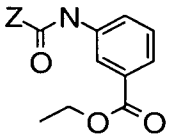
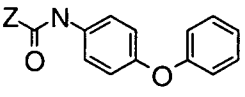
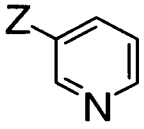
	28		37		46
	29		38		47
	30		39		48
	31		40		49
	32		41		50
	33		42		51
	34		43		52
	35		44		93
	36		45		

TABLE 2

Definition of the R^2 Moieties

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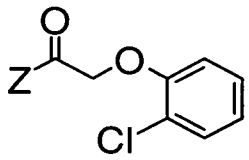
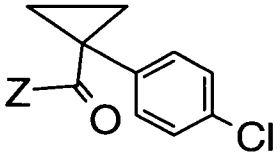
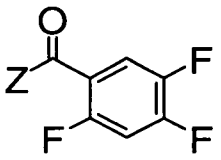
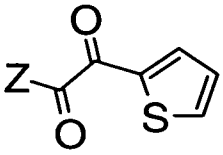
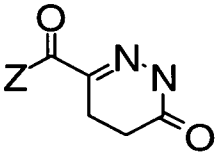
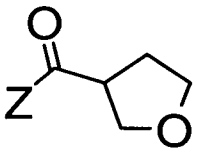
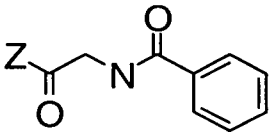
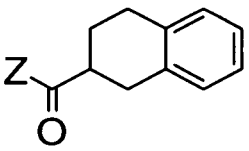
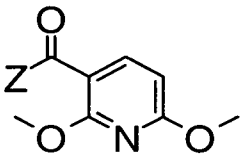
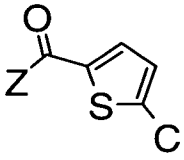
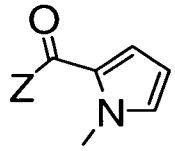
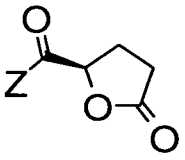
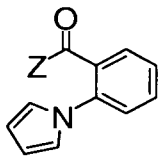
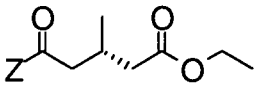
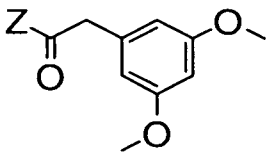
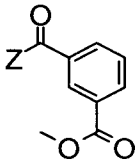
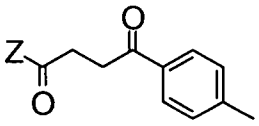
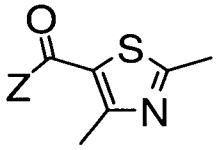
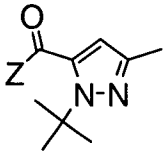
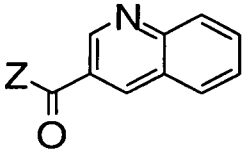
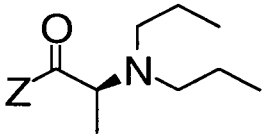
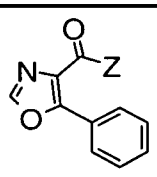
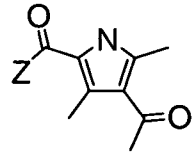
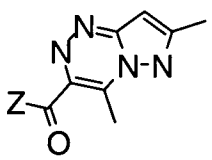
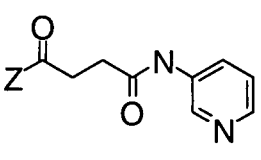
	1		10		19
	2		11		20
	3		12		21
	4		13		22
	5		14		23
	6		15		24
	7		16		25
	8		17		26
	9		18		27

TABLE 2 – Continued

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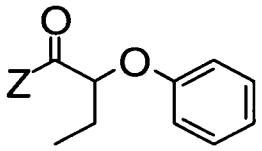
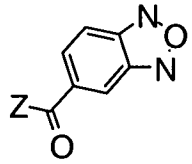
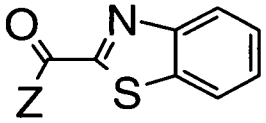
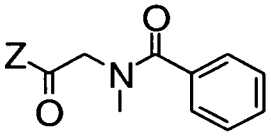
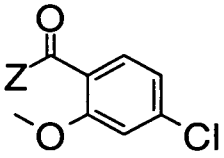
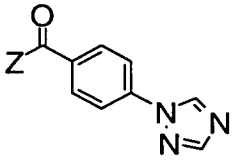
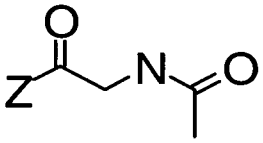
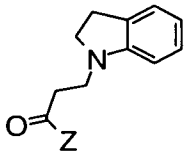
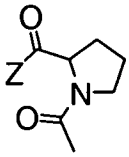
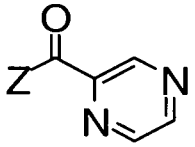
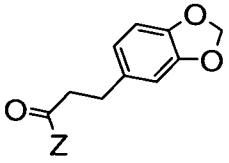
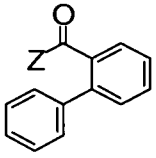
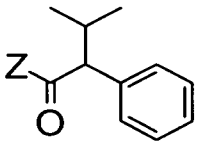
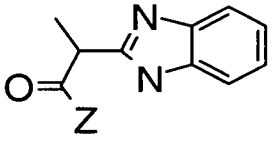
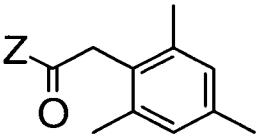
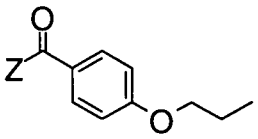
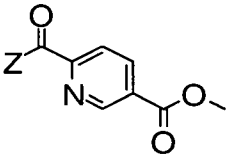
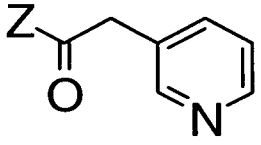
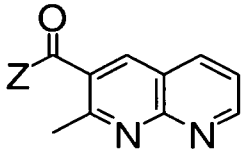
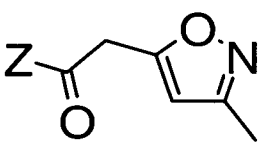
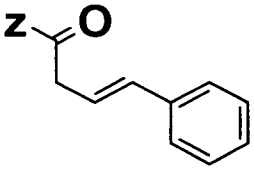
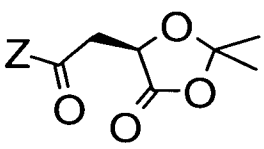
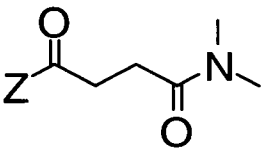
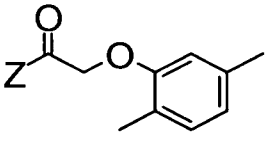
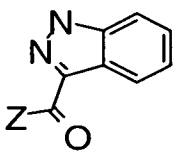
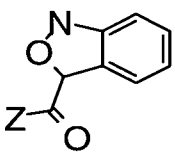
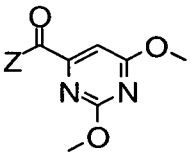
	28		37		46
	29		38		47
	30		39		48
	31		40		49
	32		41		50
	33		42		51
	34		43		52
	35		44		53
	36		45		54

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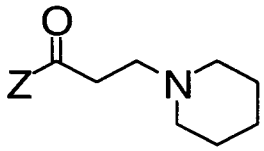
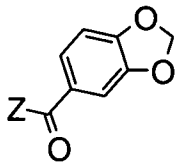
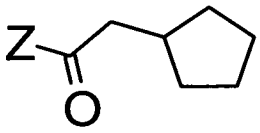
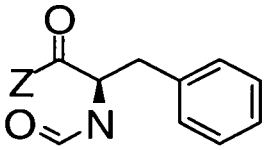
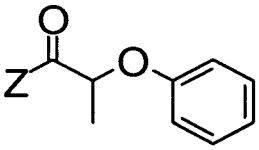
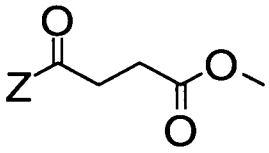
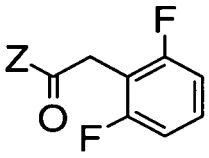
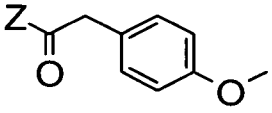
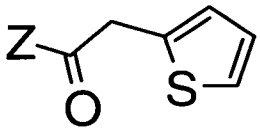
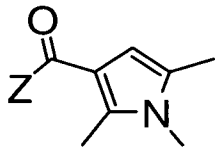
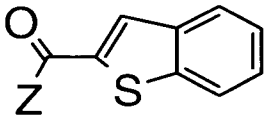
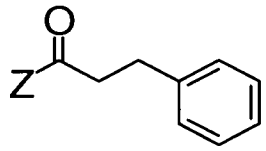
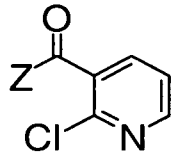
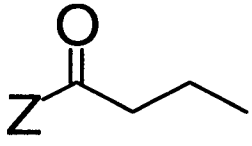
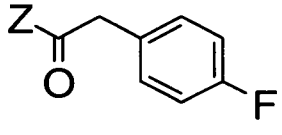
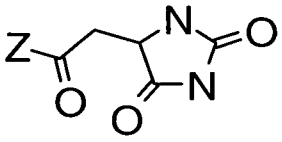
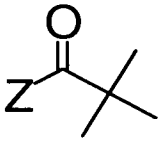
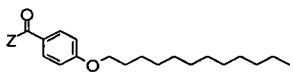
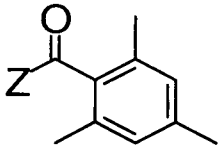
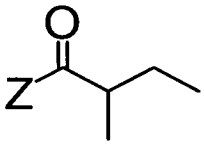
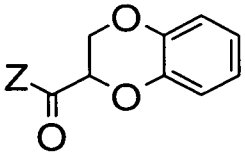
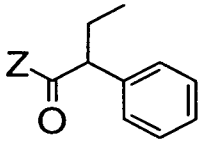
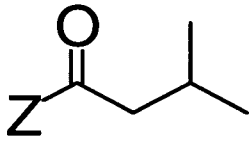
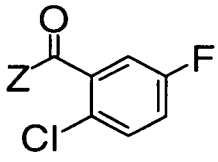
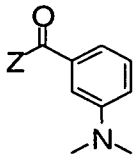
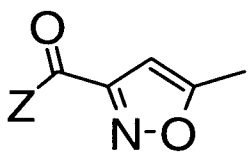
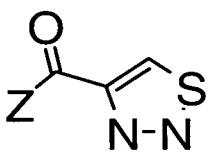
	55		64		73
	56		65		74
	57		66		75
	58		67		76
	59		68		77
	60		69		78
	61		70		79
	62		71		80
	63		72		81

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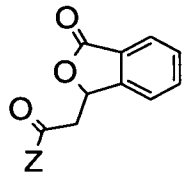
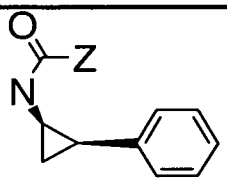
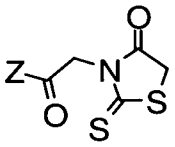
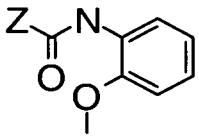
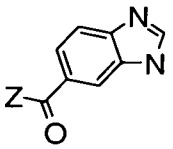
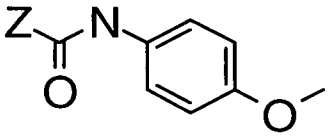
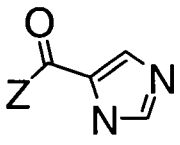
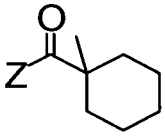
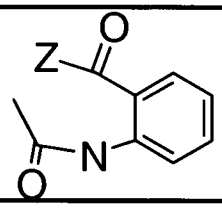
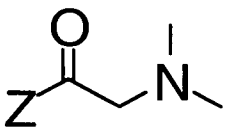
	82		133
	83		134
	84		135
	85		
	86		
	87		
	88		

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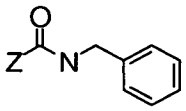
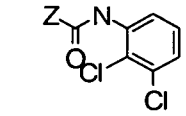
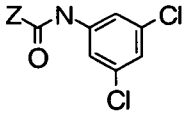
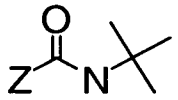
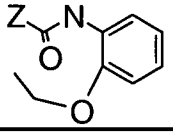
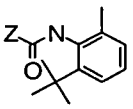
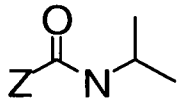
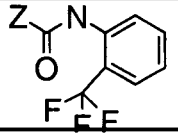
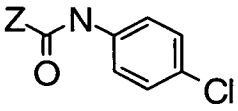
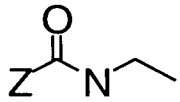
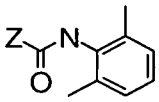
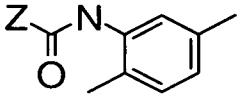
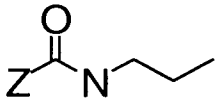
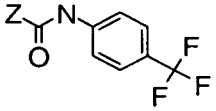
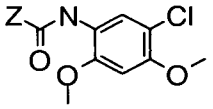
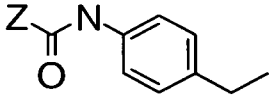
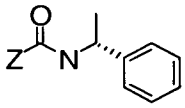
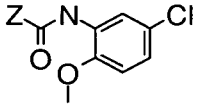
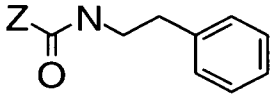
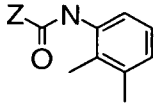
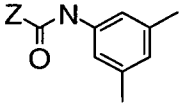
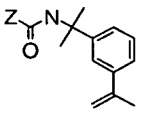
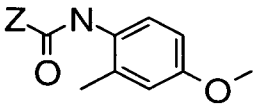
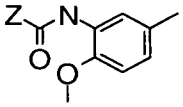
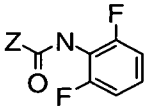
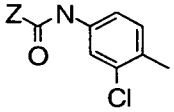
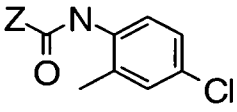
	136		145		154
	137		146		155
	138		147		156
	139		148		157
	140		149		158
	141		150		159
	142		151		160
	143		152		161
	144		153		162

TABLE 2 – Continued

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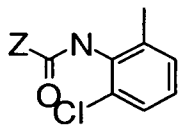
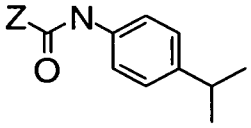
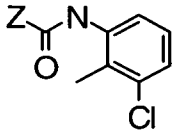
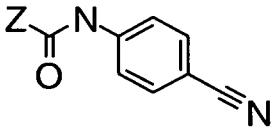
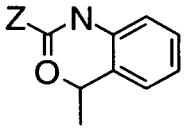
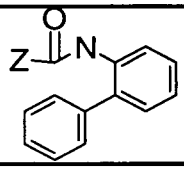
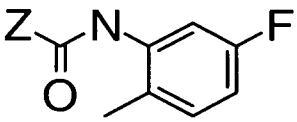
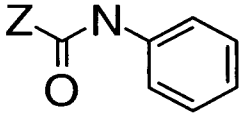
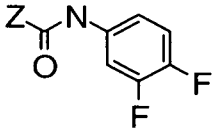
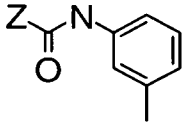
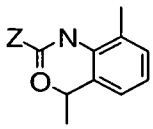
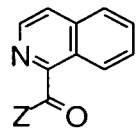
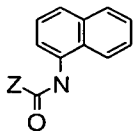
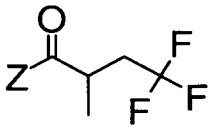
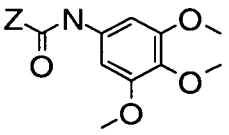
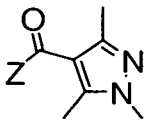
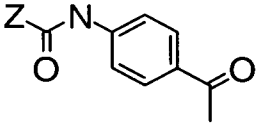
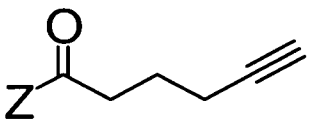
	163		172
	164		173
	165		174
	166		175
	167		176
	168		177
	169		178
	170		179
	171		180

TABLE 2 – Continued

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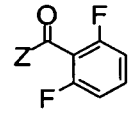
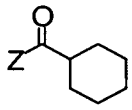
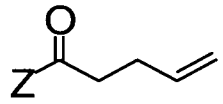
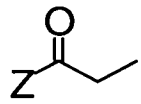
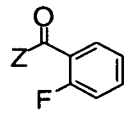
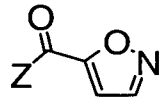
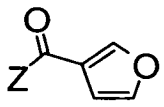
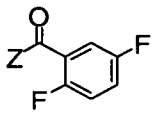
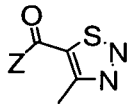
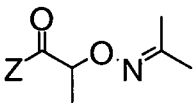
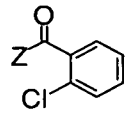
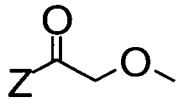
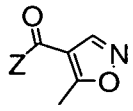
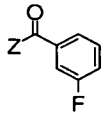
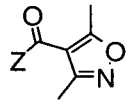
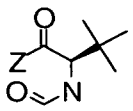
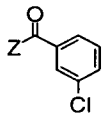
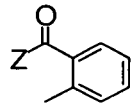
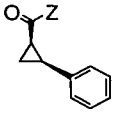
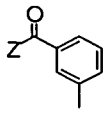
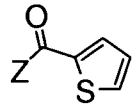
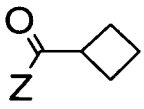
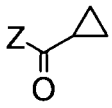
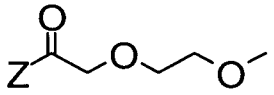
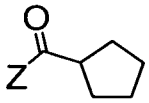
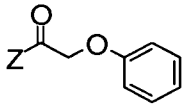
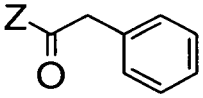
	181		190		199
	182		191		200
	183		192		201
	184		193		202
	185		194		203
	186		195		204
	187		196		205
	188		197		206
	189		198		207

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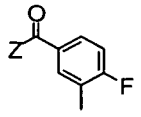
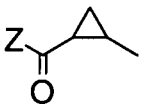
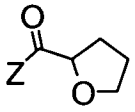
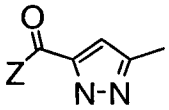
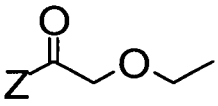
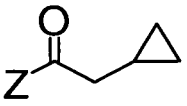
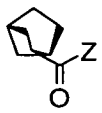
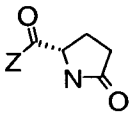
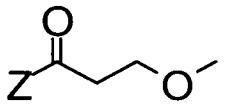
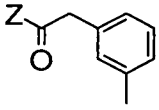
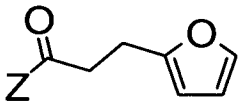
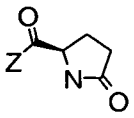
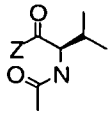
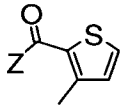
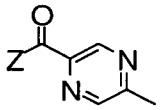
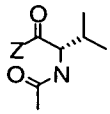
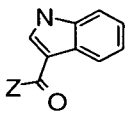
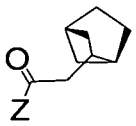
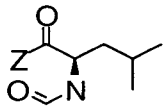
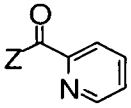
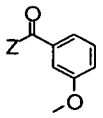
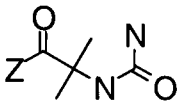
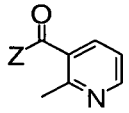
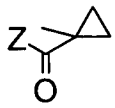
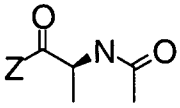
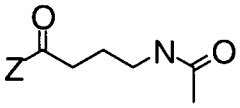
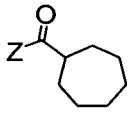
	208		217		226
	209		218		227
	210		219		228
	211		220		229
	212		221		230
	213		222		231
	214		223		232
	215		224		233
	216		225		234

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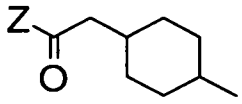
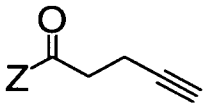
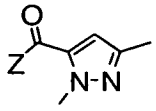
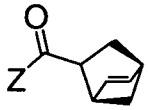
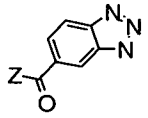
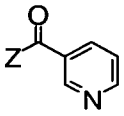
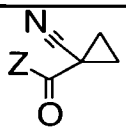
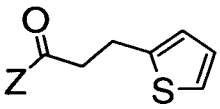
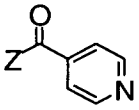
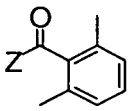
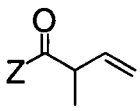
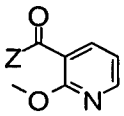
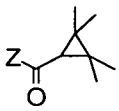
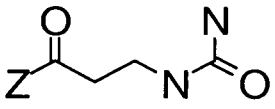
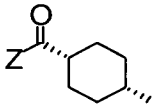
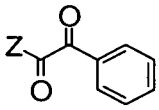
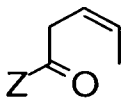
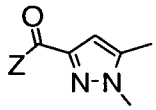
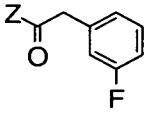
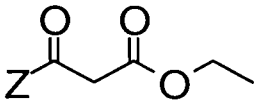
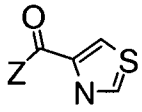
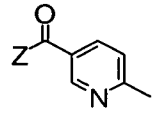
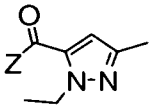
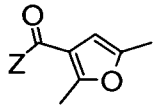
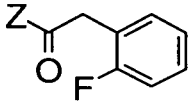
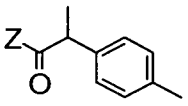
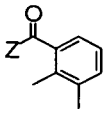
	235		244		253
	236		245		254
	237		246		255
	238		247		256
	239		248		257
	240		249		258
	241		250		259
	242		251		260
	243		252		261

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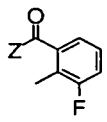
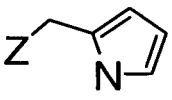
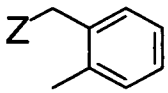
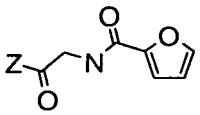
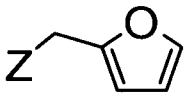
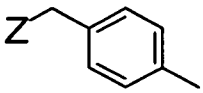
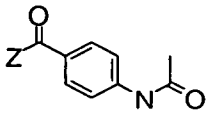
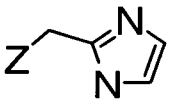
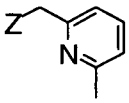
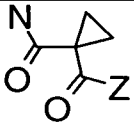
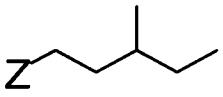
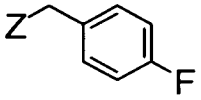
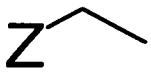
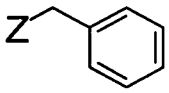
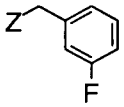
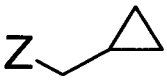
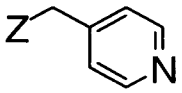
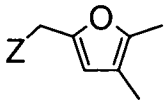
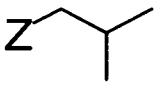
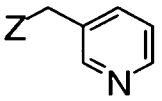
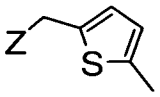
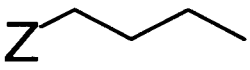
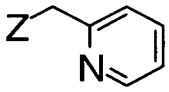
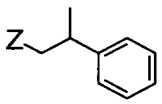
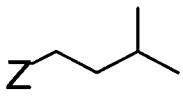
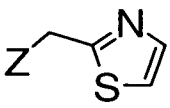
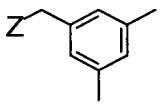
	262		271		280
	263		272		281
	264		273		282
	265		274		283
	266		275		284
	267		276		285
	268		277		286
	269		278		287
	270		279		288

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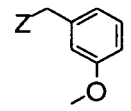
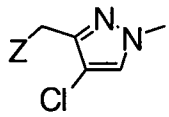
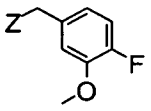
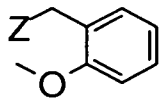
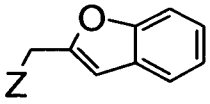
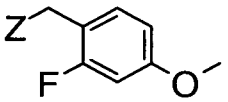
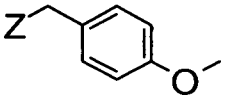
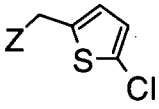
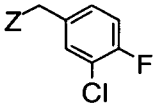
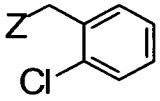
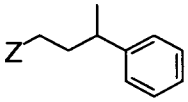
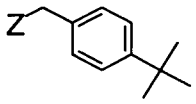
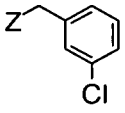
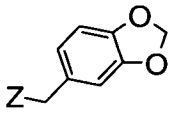
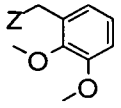
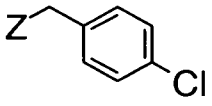
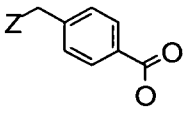
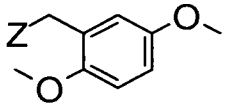
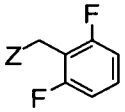
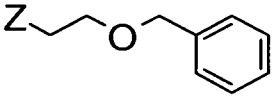
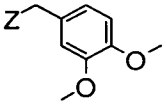
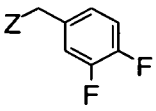
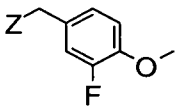
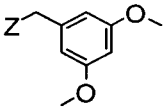
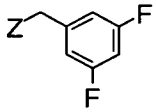
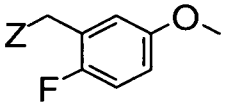
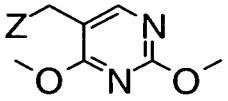
	289		298		307
	290		299		308
	291		300		309
	292		301		310
	293		302		311
	294		303		312
	295		304		313
	296		305		314
	297		306		315

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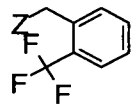
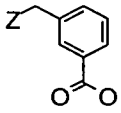
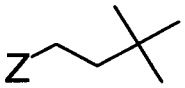
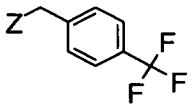
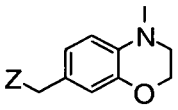
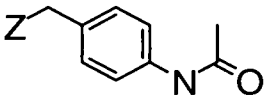
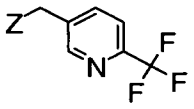
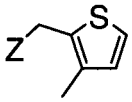
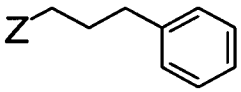
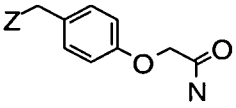
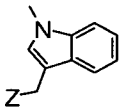
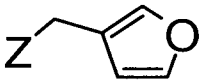
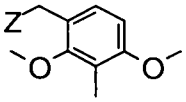
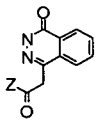
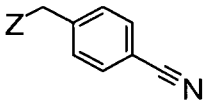
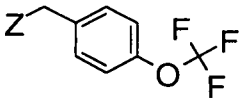
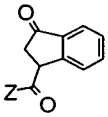
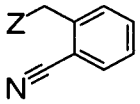
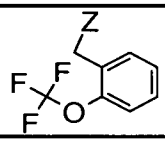
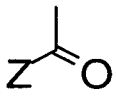
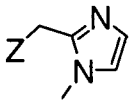
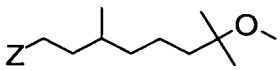
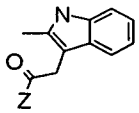
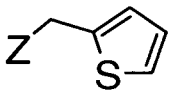
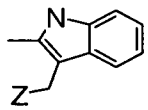
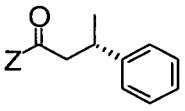
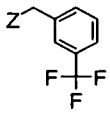
	316		325		334
	317		326		335
	318		327		336
	319		328		337
	320		329		338
	321		330		339
	322		331		340
	323		332		341
	324		333		342

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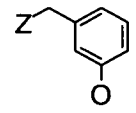
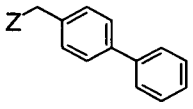
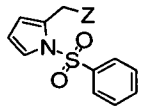
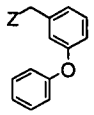
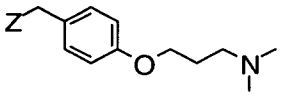
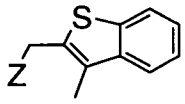
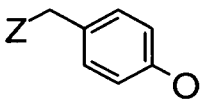
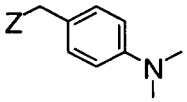
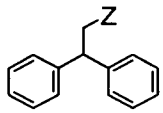
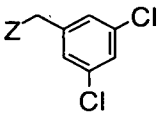
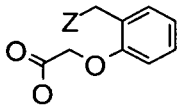
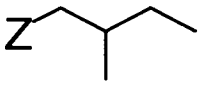
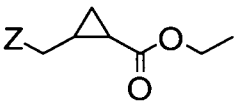
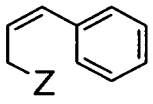
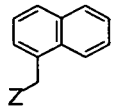
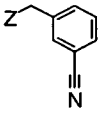
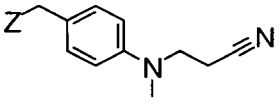
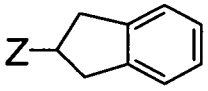
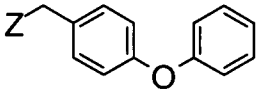
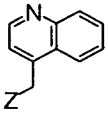
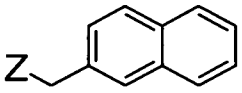
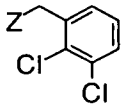
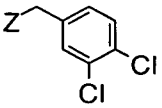
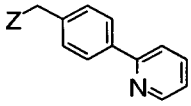
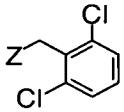
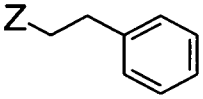
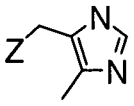
	343		352		361
	344		353		362
	345		354		363
	346		355		364
	347		356		365
	348		357		366
	349		358		367
	350		359		368
	351		360		369

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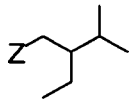
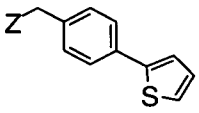
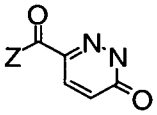
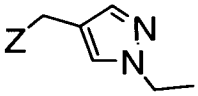
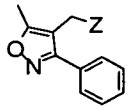
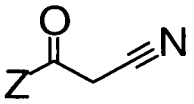
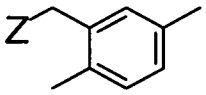
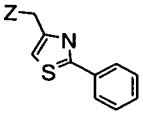
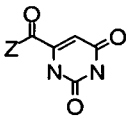
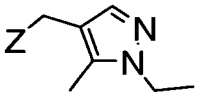
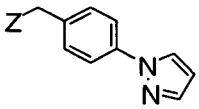
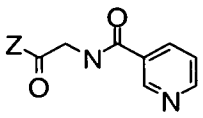
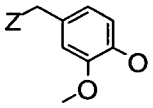
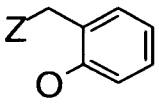
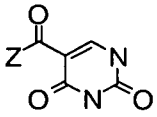
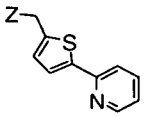
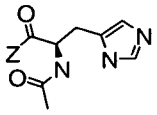
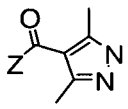
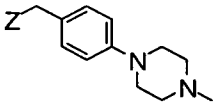
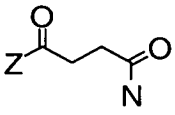
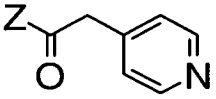
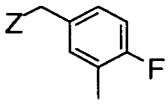
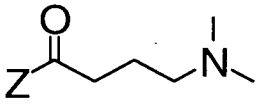
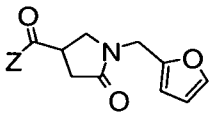
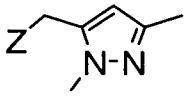
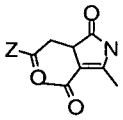
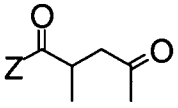
	370		379		388
	371		380		389
	372		381		390
	373		382		391
	374		383		392
	375		384		393
	376		385		394
	377		386		395
	378		387		396

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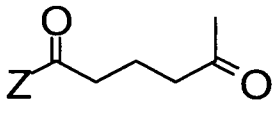
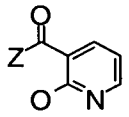
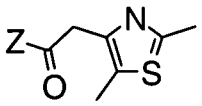
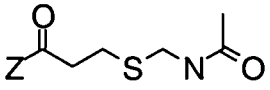
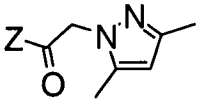
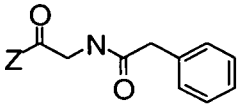
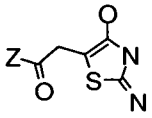
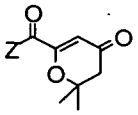
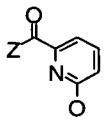
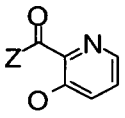
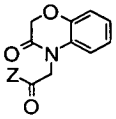
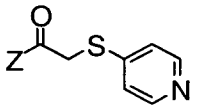
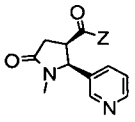
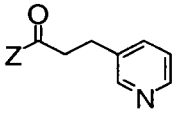
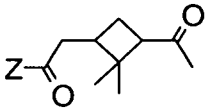
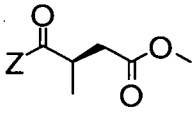
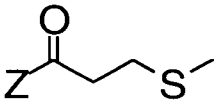
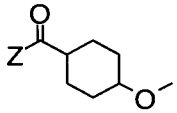
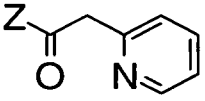
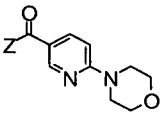
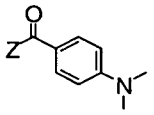
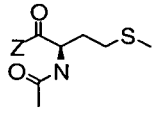
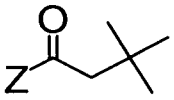
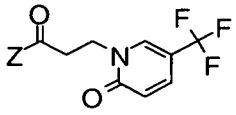
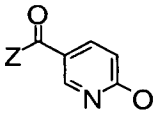
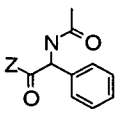
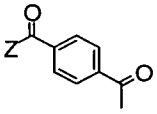
	397		406		415
	398		407		416
	399		408		417
	400		409		418
	401		410		419
	402		411		420
	403		412		421
	404		413		422
	405		414		423

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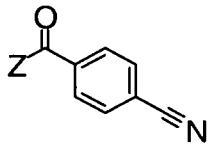
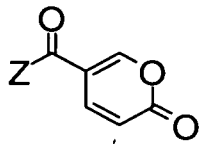
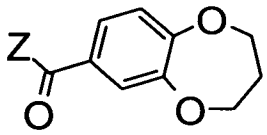
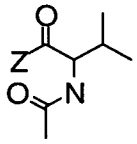
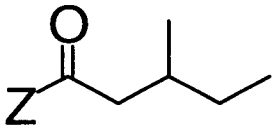
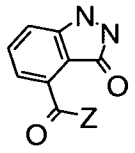
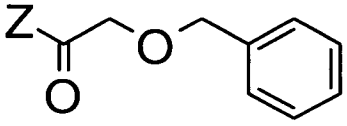
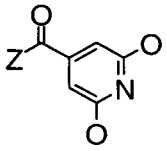
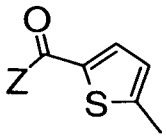
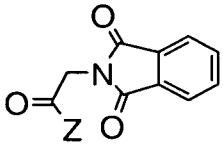
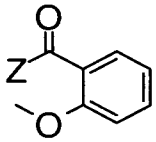
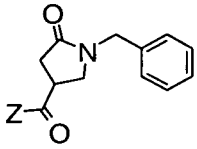
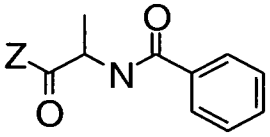
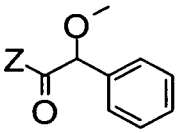
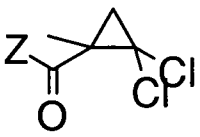
	424		433
	425		434
	426		435
	427		436
	428		437
	429		438
	430		
	431		
	432		

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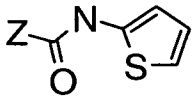
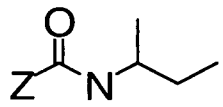
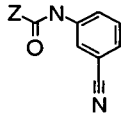
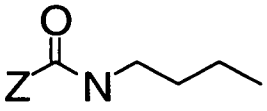
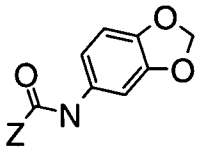
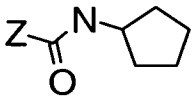
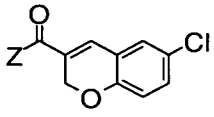
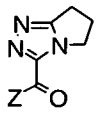
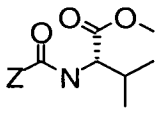
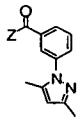
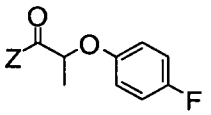
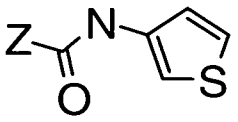
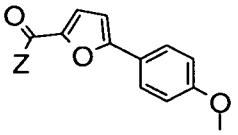
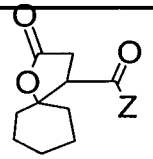
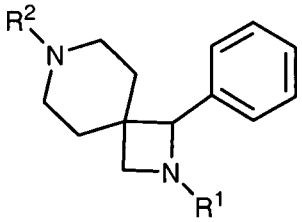
	468		474		
	469		475		
	470		476		
	471		531		534
	472		532		535
	473		533		536

Table 3a

Table 3a is directed to compounds of the formula (IA):



(IA)

wherein R^1 and R^2 are as defined in Table 3a.

An "X" in the box formed by the intersection of the R^2 and the R^1 row represents an R^2 and R^1 combination of a compound of formula IA that is included in the definition of the compounds of formula I that are useful in the methods of this invention. For example, compounds of formula IA wherein R^2 is moiety 1 (see Table 2 for definition) and R^1 is moiety 2 (see Table 1 for definition) are included in the

definition of formula I (there is an "X" in the box formed by the intersection of the R^2 column and the R^1 row).

If there is no "X" in the box, then that compound is not included in the definition of the compounds of formula I. For example, compounds of formula IA wherein moiety R^2 is 2 and moiety R^1 is 23 (no "X" in the box formed by the intersection of the R^2 column and the R^1 row) are not within the definition of the compounds of formula I.

TABLE 3a

R2 \ R1	2	3	9	10	11	14	15	23	20
1	X	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X		X
3		X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X	X
5	X	X						X	X
6	X	X	X	X	X	X	X	X	X
7	X	X	X	X	X	X	X		X
8	X	X	X	X	X	X	X	X	X
9	X	X	X	X	X	X	X		X
10	X	X	X	X	X	X	X	X	X
11	X	X	X	X	X	X	X	X	X
12	X	X	X	X	X	X	X	X	X
13	X	X	X	X		X	X	X	X
14	X	X	X	X	X	X	X	X	X
15	X	X	X	X	X	X	X	X	X
16	X	X	X	X	X	X	X	X	X
17	X	X	X	X	X	X	X	X	X
18	X	X	X	X	X	X	X	X	X
19	X	X	X	X	X	X	X	X	X
20	X	X	X	X	X	X	X		X
21	X	X	X	X	X	X	X	X	X
22	X	X	X	X	X	X	X	X	X
23	X	X	X	X	X	X	X	X	X
24	X	X	X	X	X	X	X	X	X
25	X	X	X	X	X	X	X	X	X
26	X	X	X	X	X	X	X	X	X
27	X	X		X	X	X	X		
28	X	X	X	X	X	X	X	X	X
29	X	X	X	X	X	X	X	X	X
30	X	X	X	X	X	X	X	X	X
31	X	X	X	X		X	X	X	X
32	X	X	X	X	X	X	X	X	X
33	X	X	X	X	X	X	X	X	X
34	X	X	X	X	X	X	X	X	X
35	X		X	X	X	X	X	X	X
36	X	X	X	X	X	X	X	X	X
37	X	X	X	X	X	X	X	X	X
38	X	X	X	X	X	X	X	X	X
39	X	X	X	X	X		X	X	X
40	X	X	X	X	X	X	X	X	X
41	X			X	X		X	X	X
42	X	X	X	X	X	X	X	X	X
43	X	X	X	X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1	22	27	38	39	40	41	42	31	32	34	35	36	37
1	X	X	X	X	X	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X	X	X	X	X	X
5	X	X	X	X	X		X	X		X	X	X	X
6	X	X	X	X	X	X	X	X	X	X	X	X	X
7	X	X	X	X	X	X	X	X	X	X	X	X	X
8	X	X	X	X	X	X	X	X	X	X	X	X	X
9	X		X	X	X	X	X	X	X	X	X	X	X
10	X	X	X	X	X	X	X	X	X	X	X	X	X
11	X	X	X	X	X	X	X	X	X	X	X	X	X
12	X	X	X	X	X	X	X	X	X	X	X	X	X
13	X	X	X	X	X	X	X	X	X	X	X	X	X
14	X	X	X	X	X	X	X	X	X	X	X	X	X
15	X	X	X	X	X	X	X	X	X	X	X	X	X
16	X	X	X	X	X	X	X	X	X	X	X	X	X
17	X	X	X	X	X	X	X	X	X	X	X	X	X
18	X	X	X	X		X	X	X	X	X	X	X	X
19	X	X	X	X	X	X			X		X	X	X
20	X	X	X	X	X	X	X	X	X	X	X	X	X
21	X	X	X	X	X	X	X	X	X	X	X	X	X
22	X	X	X	X	X	X	X	X	X	X	X	X	X
23	X	X	X	X	X	X	X	X	X	X	X	X	X
24	X	X	X	X	X	X	X	X	X	X	X	X	X
25	X	X	X	X	X	X	X	X	X	X	X	X	X
26	X	X	X	X	X	X	X	X	X	X	X	X	X
27													
28	X	X	X	X	X	X	X	X	X	X	X	X	X
29	X	X	X	X	X	X	X	X	X	X	X	X	X
30	X		X	X	X	X	X	X	X	X	X	X	X
31	X	X	X	X	X	X	X	X	X	X	X	X	X
32	X	X	X	X	X	X	X	X	X	X		X	X
33	X	X	X	X	X	X	X		X	X	X	X	X
34	X	X	X	X	X	X		X	X	X		X	X
35	X		X	X		X		X				X	X
36	X	X	X	X	X	X	X	X	X	X	X	X	X
37	X	X	X	X	X	X	X	X	X	X	X	X	X
38	X	X	X	X	X	X	X	X	X	X	X	X	X
39	X	X	X	X	X	X	X	X	X	X	X	X	X
40	X	X	X	X			X	X	X	X	X	X	X
41	X	X	X	X	X	X	X	X	X	X	X	X	X
42	X	X	X	X	X		X	X	X	X	X	X	X
43	X	X	X	X	X		X	X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1	30	44	45	47	49	50	51	52	7	8	13
1											
2	X										
3	X	X	X	X	X	X	X	X			
4											
5	X	X	X	X	X	X	X	X			
6	X								X	X	X
7	X								X	X	X
8	X								X	X	X
9	X								X	X	X
10	X								X	X	X
11	X								X	X	X
12	X								X	X	X
13	X								X	X	X
14	X								X	X	X
15	X								X	X	X
16	X	X	X	X	X	X	X	X	X	X	X
17	X								X	X	X
18	X								X	X	X
19									X	X	X
20	X	X	X	X	X	X	X	X	X	X	X
21	X								X	X	X
22	X	X	X	X	X	X	X	X	X	X	X
23	X								X	X	X
24	X								X	X	X
25	X								X	X	X
26	X								X	X	X
27									X	X	X
28	X								X	X	X
29	X								X	X	X
30	X	X	X	X	X	X	X	X	X	X	X
31	X								X	X	X
32	X								X	X	X
33									X	X	X
34	X								X	X	X
35	X		X	X		X	X	X	X	X	X
36	X								X	X	X
37	X								X	X	X
38	X								X	X	X
39	X								X	X	X
40	X								X	X	X
41	X								X	X	X
42	X								X	X	X
43	X								X	X	X

TABLE 3a – Continued

R2 \ R1	2	3	9	10	11	14	15	23	20
44	X	X	X	X	X	X	X		X
45	X	X	X	X	X	X	X	X	X
46					X	X	X	X	X
47	X	X	X	X	X	X	X	X	X
48	X	X	X	X	X	X	X	X	X
49	X	X	X		X	X	X	X	X
50	X	X	X	X	X	X	X	X	X
51	X	X		X	X	X	X		
52	X	X	X	X	X	X	X	X	X
53	X	X	X	X	X	X	X	X	X
54	X	X	X	X	X	X	X	X	X
55	X	X	X	X	X	X	X	X	X
56	X	X	X	X	X	X	X	X	X
57	X	X	X	X	X	X	X	X	X
58	X	X	X	X	X	X	X	X	X
59	X	X	X	X	X	X	X	X	X
60	X	X	X	X	X	X	X	X	X
61	X	X	X	X	X	X	X	X	X
62	X	X	X	X	X	X	X	X	X
63	X	X	X	X	X	X	X	X	X
64	X	X	X	X		X	X	X	X
65	X	X	X	X	X	X	X	X	X
66	X	X	X	X	X	X	X	X	X
67	X	X	X	X	X	X	X	X	X
68	X	X	X	X	X	X	X	X	X
69	X	X	X	X	X	X	X	X	X
70	X	X	X	X	X	X	X	X	X
71	X	X	X	X		X	X	X	X
72	X	X	X	X	X	X	X	X	X
73	X	X	X	X	X	X	X	X	X
74	X	X	X	X	X	X	X	X	X
75	X	X	X	X		X	X	X	X
76	X	X	X	X	X	X	X	X	X
77	X	X	X	X		X	X	X	X
78	X	X	X	X	X	X	X		
79	X	X	X	X	X	X	X	X	X
80	X	X	X	X	X	X	X	X	X
81	X	X	X			X		X	X
82	X	X	X	X	X	X	X	X	X
83		X		X	X			X	X
84			X	X	X	X		X	X
85			X		X			X	X
86					X				X
87			X		X				X
88					X			X	X

TABLE 3a - Continued

R2 \ R1	22	27	38	39	40	41	42	31	32	34	35	36	37
44	X		X	X	X	X	X	X	X	X	X	X	X
45	X	X	X	X	X	X	X	X	X	X	X	X	X
46	X	X		X	X		X	X	X		X		
47	X	X		X	X		X	X	X	X	X	X	
48	X		X	X	X	X	X	X	X	X	X	X	X
49	X	X	X	X	X		X	X	X	X	X	X	X
50	X	X	X	X	X	X	X	X	X	X	X	X	X
51		X		X	X	X	X	X	X	X	X		
52	X	X	X	X	X	X	X	X	X	X	X	X	X
53	X	X	X	X	X	X	X	X	X	X	X	X	X
54	X	X	X	X	X	X	X	X	X	X	X	X	X
55	X	X	X	X	X	X	X	X	X	X	X	X	X
56	X	X											
57	X	X	X	X	X		X		X	X	X	X	X
58	X	X		X	X		X	X	X	X	X	X	
59	X	X	X	X	X		X	X	X	X	X	X	X
60	X		X	X	X	X	X	X	X	X	X	X	X
61	X	X		X	X		X	X	X	X	X	X	
62	X	X	X	X	X	X	X	X	X	X	X	X	X
63	X	X	X	X	X	X	X	X	X	X	X	X	X
64	X	X	X	X	X		X	X	X	X	X	X	X
65	X	X	X	X	X		X		X	X	X	X	X
66	X	X	X	X	X		X	X	X	X	X	X	X
67	X	X	X	X	X		X	X	X	X	X	X	X
68	X	X	X	X	X		X	X	X	X	X	X	
69	X	X		X	X		X	X	X	X	X		
70	X	X		X	X		X	X	X	X	X	X	
71	X	X		X	X		X	X	X	X	X	X	
72	X	X	X	X	X		X	X	X	X	X	X	
73	X	X	X	X	X		X	X	X	X	X		X
74	X	X	X	X	X		X	X	X	X	X	X	
75	X	X	X	X	X		X	X	X	X	X	X	X
76	X	X	X	X	X		X	X	X	X	X	X	X
77	X	X	X	X	X	X	X	X	X	X	X	X	
78													
79	X	X	X	X	X		X	X	X	X	X	X	X
80	X	X	X	X	X		X	X	X	X	X	X	X
81	X	X	X	X	X	X	X		X	X	X	X	X
82	X	X	X	X	X	X	X			X	X	X	X
83	X		X	X		X		X					X
84	X	X	X	X	X		X		X		X	X	X
85	X	X	X	X		X		X				X	X
86	X	X	X	X		X				X			X
87	X		X	X		X		X					X
88	X	X	X	X		X		X					X

TABLE 3a - Continued

R2 \ R1	30	44	45	47	49	50	51	52	7	8	13
44	X	X	X	X	X	X	X	X	X	X	X
45	X								X	X	X
46	X								X	X	X
47	X	X	X	X	X	X	X	X	X	X	X
48	X	X	X	X	X	X	X	X	X	X	X
49	X								X	X	X
50	X								X	X	X
51	X								X	X	X
52	X								X	X	X
53	X								X	X	X
54	X								X	X	X
55	X	X	X	X	X	X	X	X	X	X	X
56									X	X	X
57									X	X	X
58	X								X	X	X
59	X	X	X	X	X	X	X	X	X	X	X
60	X	X	X	X	X		X	X	X	X	X
61	X								X	X	X
62	X								X	X	X
63	X								X	X	X
64	X	X	X	X	X	X	X	X	X	X	X
65	X								X	X	X
66	X								X	X	X
67	X								X	X	X
68	X	X	X	X	X	X	X	X	X	X	X
69	X								X	X	X
70	X								X	X	X
71	X								X	X	X
72	X								X	X	X
73	X								X	X	X
74	X								X	X	X
75	X								X	X	X
76	X								X	X	X
77	X								X	X	X
78									X	X	X
79	X								X	X	X
80	X								X	X	X
81	X								X	X	X
82	X								X	X	X
83		X		X			X	X			
84	X	X	X	X	X	X	X	X			
85	X	X		X	X	X	X	X	X	X	X
86									X	X	X
87	X								X	X	X
88											

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	20	22	
133	X	X	X	X	X	X		X	X	
134	X	X	X	X	X	X		X	X	
135	X	X	X	X	X	X		X	X	
136	X	X	X	X	X	X		X	X	
137	X	X	X	X	X	X		X	X	
138	X	X	X	X	X	X		X	X	
139	X	X	X	X	X				X	
140	X	X	X	X	X				X	
141	X	X	X	X					X	
142	X	X	X	X	X	X		X	X	
143	X	X	X	X	X	X		X	X	
144	X	X	X	X	X	X		X	X	
145	X	X	X		X	X		X	X	
146	X	X	X	X	X	X		X	X	
147	X	X	X		X				X	
148	X	X	X	X	X	X		X	X	
149	X	X	X	X	X	X		X	X	
150	X	X	X	X	X	X		X	X	
151	X	X	X	X	X	X		X	X	
152	X	X	X	X	X	X		X	X	
153	X	X	X	X		X		X	X	
154	X	X	X	X		X		X	X	
155	X	X	X	X	X	X		X	X	
156	X	X	X	X	X	X		X	X	
157	X	X	X	X	X	X		X	X	
158	X	X	X	X	X	X		X	X	
159	X	X	X	X	X	X		X	X	
160	X	X	X	X	X	X		X	X	
161	X	X	X	X	X	X		X	X	
162	X	X	X	X	X	X		X	X	
163	X	X	X	X	X	X		X	X	
164	X	X	X	X	X	X		X	X	
165	X	X	X	X	X	X		X	X	
166	X	X	X	X	X	X		X	X	
167	X	X	X	X	X	X		X	X	
168	X	X	X	X	X	X		X	X	
169	X		X						X	
170	X		X						X	
171	X		X						X	
172	X		X	X	X	X		X	X	
173	X		X			X		X	X	
174	X		X						X	
175	X		X		X	X		X	X	
176	X		X	X	X	X		X	X	

TABLE 3a - Continued

R2 \ R1	44	45	47	49	50	51	52	7	8	13	17	19	21
133			X		X	X		X	X	X			X
134		X	X		X	X	X	X	X	X			X
135		X	X		X	X	X	X	X	X			X
136		X	X		X	X	X	X	X	X			X
137								X	X	X			X
138		X	X		X	X	X	X	X	X			X
139		X	X		X	X	X	X	X	X			X
140		X	X		X	X		X	X	X			X
141		X	X		X	X	X	X	X	X			
142								X	X	X			X
143								X	X	X			X
144		X	X		X	X	X	X	X	X			X
145								X	X	X			X
146		X			X	X	X	X	X	X			X
147								X	X	X			X
148								X	X	X			X
149								X	X	X			X
150								X	X	X			X
151								X	X	X			X
152		X	X		X	X	X	X	X	X			X
153									X	X			X
154									X	X			X
155								X	X	X			X
156								X	X	X			X
157		X	X		X	X	X	X	X	X			X
158								X	X	X			X
159								X	X	X			X
160									X	X			X
161								X	X	X			X
162								X	X	X			X
163								X	X	X			X
164								X	X	X			X
165								X	X	X			X
166								X	X	X			X
167		X	X		X	X	X	X	X	X			X
168								X	X	X			X
169									X	X			
170									X	X			X
171									X	X			
172								X	X	X			X
173									X	X			X
174									X	X			
175		X	X		X	X	X	X	X	X			X
176								X	X	X			X

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23	
180	X		X	X		X	X	X	
181	X		X	X	X	X	X	X	
182	X		X	X		X		X	
183	X		X	X	X	X	X	X	
184	X		X	X	X	X	X	X	
185	X		X	X		X	X	X	
186	X		X			X		X	
187	X		X	X	X	X	X	X	
188	X		X	X	X	X	X	X	
190	X		X		X	X	X	X	
191	X		X		X	X	X	X	
192	X		X	X	X	X	X	X	
193	X		X		X	X	X	X	
194	X		X	X	X	X	X	X	
195	X		X	X	X	X	X	X	
196	X		X	X	X	X	X	X	
197	X		X	X	X	X	X	X	
199	X		X	X	X	X	X	X	
201	X		X	X	X	X		X	
203	X		X	X	X	X	X	X	
204	X		X	X	X	X	X	X	
205	X		X	X	X	X	X	X	
206	X		X	X	X	X		X	
207	X		X	X	X	X	X	X	
208	X		X	X	X	X	X	X	
209	X		X	X	X	X		X	
210	X		X	X	X	X	X	X	
211	X		X	X	X	X	X	X	
212	X		X	X	X	X	X	X	
213	X		X	X	X	X		X	
214	X		X	X	X	X	X	X	
215	X		X			X	X	X	
216	X		X	X	X	X	X	X	
220	X		X	X	X	X	X	X	
221	X		X	X	X	X	X	X	
222	X		X			X	X	X	
228	X		X	X	X	X	X	X	
229	X		X	X	X	X	X	X	
231	X		X	X	X	X	X	X	
232	X		X	X	X	X	X	X	
233	X		X	X	X	X	X	X	
234	X		X	X	X	X	X	X	
235	X		X	X	X	X	X	X	

TABLE 3a - Continued

R2 \ R1	20	22	27	38	39	40	41	42	31	32	34	35	36	37
180		X			X	X	X	X	X	X	X		X	X
181		X			X	X	X	X	X	X	X		X	X
182		X			X	X	X	X		X	X		X	X
183		X			X	X	X	X	X	X	X		X	X
184		X			X	X	X	X	X	X	X			
185														
186					X	X	X	X	X	X	X			
187		X			X	X	X	X	X	X	X		X	X
188		X			X	X	X	X	X	X	X		X	X
190		X			X	X	X	X	X	X	X		X	X
191		X			X	X	X	X	X	X	X		X	X
192		X			X	X	X	X	X	X	X		X	X
193		X			X	X	X	X	X	X	X		X	X
194		X			X	X	X	X	X	X	X		X	X
195		X			X	X	X	X	X	X	X		X	X
196		X			X	X	X	X	X	X	X		X	X
197		X			X	X	X	X	X	X	X		X	X
199		X			X	X	X	X	X	X	X		X	X
201		X					X		X	X	X		X	X
203		X			X		X		X	X	X		X	X
204		X			X	X	X	X	X	X	X		X	X
205		X			X	X	X	X	X	X	X		X	X
206		X			X	X	X	X	X	X	X		X	X
207		X			X	X	X	X	X	X	X		X	X
208		X			X	X	X	X	X	X	X		X	X
209		X					X		X	X	X			
210		X					X		X	X	X		X	X
211		X			X	X	X	X	X	X	X		X	X
212		X			X	X	X	X	X	X	X			
213		X					X		X	X	X			X
214		X			X		X	X	X	X	X		X	
215														
216		X			X	X	X	X	X	X	X		X	
220		X			X	X	X	X	X	X	X		X	X
221		X			X	X	X	X	X	X	X		X	X
222		X			X	X	X	X	X	X	X		X	X
228		X			X	X	X	X	X	X	X		X	X
229														
231					X	X	X	X	X	X	X		X	X
232		X			X	X	X	X	X	X	X		X	X
233		X			X	X	X	X	X	X	X		X	X
234		X			X	X	X	X		X	X		X	X
235					X	X	X	X	X	X	X		X	X

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	26
180			X		X	X		X	X	X
181	X		X		X	X	X		X	X
182	X		X					X	X	X
183	X		X		X	X	X	X	X	X
184	X		X		X	X		X	X	
185			X			X				
186								X		
187	X		X		X	X	X	X	X	X
188	X		X		X	X	X		X	X
190	X				X		X	X	X	X
191	X		X		X	X	X	X	X	X
192	X		X		X	X	X	X	X	
193	X		X		X	X	X	X	X	X
194	X		X		X	X	X	X	X	X
195	X		X		X	X	X	X	X	
196	X		X		X	X	X		X	
197	X		X		X	X	X	X	X	X
199	X		X		X	X	X	X	X	X
201	X		X		X	X	X	X	X	X
203	X		X		X	X	X	X		X
204	X		X		X	X	X	X	X	X
205	X		X		X	X	X		X	X
206	X		X		X	X	X	X	X	X
207	X		X		X	X	X		X	X
208	X		X		X	X	X	X	X	X
209	X		X		X	X	X	X		X
210	X				X	X	X	X		X
211	X		X		X	X	X	X	X	X
212	X		X		X	X	X	X	X	X
213	X		X		X	X	X	X	X	X
214	X		X		X	X	X	X	X	X
215										X
216	X		X		X	X	X	X	X	X
220	X		X			X	X	X	X	X
221	X		X		X	X	X		X	X
222						X	X	X	X	X
228	X		X		X	X	X	X	X	X
229	X		X		X	X	X			X
231	X		X				X	X		X
232	X		X		X	X	X		X	X
233	X		X		X		X	X	X	X
234	X		X		X	X	X		X	X
235	X		X		X	X	X	X		X

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23
237	X		X	X	X	X	X	X
238	X		X	X	X	X	X	X
239	X		X	X	X	X	X	X
240	X		X	X	X	X	X	X
241	X		X	X	X	X	X	X
243	X		X	X	X	X	X	X
244	X		X	X	X	X	X	X
246	X		X	X	X	X	X	X
247	X		X	X	X	X	X	X
249	X		X	X	X	X	X	X
250	X		X	X	X	X	X	X
252	X		X	X	X	X	X	X
253	X		X	X	X	X	X	X
254	X		X	X	X	X	X	X
255	X		X	X	X	X	X	X
256	X		X	X	X	X	X	X
257	X		X	X	X	X	X	X
259	X		X	X	X	X	X	X
261	X		X	X	X	X	X	X
262	X		X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1	20	22	27	38	39	40	41	42	31	32	34	35	36	37
237		X					X		X	X	X		X	X
238		X			X	X	X	X			X		X	X
239					X	X	X	X	X	X	X		X	X
240		X			X	X	X	X		X	X		X	X
241		X			X	X	X	X	X	X	X		X	X
243		X			X	X	X	X	X	X	X		X	X
244		X			X	X	X	X	X	X	X		X	X
246		X			X	X	X		X	X	X		X	X
247		X			X	X	X		X	X	X			
249		X			X	X	X	X	X	X	X		X	X
250		X			X	X	X	X	X	X	X		X	X
252		X			X	X	X	X	X	X	X		X	X
253							X		X	X	X			
254		X			X	X	X	X	X	X	X		X	X
255		X			X	X	X	X	X	X	X		X	X
256		X			X	X	X	X	X	X	X		X	X
257		X			X	X	X	X	X	X	X		X	X
259		X			X		X		X	X	X		X	X
261		X			X	X	X	X	X	X	X		X	X
262		X			X	X	X	X	X	X	X		X	X

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	26	28	29
237	X		X		X	X	X	X	X	X		
238	X		X		X	X	X	X	X	X		
239	X		X		X	X	X	X		X		
240	X		X		X	X	X		X	X		
241	X		X		X	X	X	X	X	X		
243	X		X		X	X	X		X	X		
244	X		X		X	X	X		X	X		
246	X		X		X	X	X	X	X	X		
247	X		X		X	X	X	X	X	X		
249	X		X		X	X	X	X		X		
250	X		X		X	X	X	X	X	X		
252	X		X		X	X	X	X	X	X		
253	X		X		X	X	X	X	X	X		
254	X		X		X	X	X	X	X	X		
255	X		X		X	X	X	X	X	X		
256	X		X		X	X	X	X	X	X		
257	X		X		X	X	X	X		X		
259	X		X		X	X	X	X	X	X		
261	X		X		X	X	X	X	X	X		
262	X		X		X	X	X	X		X		

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23
265								
266	X	X	X	X	X	X	X	X
267	X	X	X	X	X	X	X	X
268	X	X	X	X	X	X	X	X
269	X	X	X	X		X	X	X
270	X	X	X	X	X	X	X	X
271	X	X	X	X	X	X		X
272	X	X	X	X	X	X		X
273	X	X	X	X	X	X		X
274			X					
275	X	X	X	X	X		X	X
276	X	X	X	X	X	X		X
277	X	X		X	X	X	X	X
278	X	X	X	X	X	X	X	X
279	X	X	X	X	X	X	X	X
280	X	X	X	X	X	X		X
281	X	X	X	X	X	X		X
282	X	X	X	X	X	X	X	X
283	X	X	X	X	X	X		X
284	X	X	X	X	X	X	X	X
285	X	X	X	X	X	X		X
286	X	X	X		X			
287	X	X		X	X			X
288	X	X	X	X	X	X		X
289	X	X	X	X	X			X
290	X	X	X	X	X			X
291	X	X	X	X				X
292	X	X	X	X	X	X		X
293	X	X	X	X	X	X		X
294	X	X	X		X			X
295	X	X	X	X	X	X	X	X
296	X	X	X	X	X	X		X
297	X	X	X	X	X	X	X	X
298	X	X	X	X	X		X	X
299	X	X						X

TABLE 3a - Continued

R2 \ R1	20	22	27	38	39	40	41	42	31	32	34	35	36	37
265														
266				X	X	X	X	X			X	X		
267		X		X	X	X	X	X	X	X	X	X	X	X
268		X		X	X	X	X	X	X	X	X	X	X	X
269		X		X	X	X	X	X	X	X	X	X	X	X
270		X		X	X	X	X		X	X	X	X	X	X
271		X		X		X	X		X	X	X	X	X	X
272		X		X	X		X	X	X	X	X		X	X
273		X		X	X	X	X	X	X	X	X	X	X	X
274		X								X				
275		X			X	X	X	X	X	X	X	X	X	X
276		X		X	X	X	X	X	X	X	X	X	X	X
277		X			X	X	X	X	X	X	X	X	X	
278		X			X	X	X	X	X	X	X	X	X	X
279		X		X	X	X	X	X	X	X	X	X	X	X
280		X			X	X	X	X	X		X	X	X	
281		X		X	X	X	X	X	X	X	X	X	X	X
282		X		X	X	X	X	X	X	X	X	X	X	X
283		X		X		X	X	X	X	X	X	X	X	X
284		X		X	X	X	X	X	X	X	X	X	X	X
285		X		X	X		X	X		X		X	X	X
286		X						X		X	X		X	X
287		X		X		X	X	X	X			X	X	
288		X		X	X	X	X	X	X	X	X	X	X	X
289		X		X	X	X	X	X	X		X	X	X	X
290		X		X	X	X		X	X	X	X		X	
291		X		X	X	X		X	X	X	X	X	X	
292		X		X	X	X	X	X	X	X	X	X	X	
293		X		X	X	X	X	X	X	X	X	X	X	X
294		X		X	X	X	X		X	X	X	X	X	X
295		X		X	X	X		X	X	X	X	X	X	X
296		X		X	X	X	X	X	X	X	X	X	X	
297		X		X	X	X	X	X	X	X	X	X	X	X
298		X		X	X	X	X	X	X	X	X	X	X	X
299		X					X	X		X				

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	26	28	29	30
265													
266		X	X	X		X					X		X
267	X	X	X	X	X	X	X	X			X	X	X
268	X	X	X	X	X	X	X	X			X	X	X
269	X	X	X		X	X		X			X	X	X
270	X	X	X		X	X	X	X			X	X	X
271	X	X	X	X	X	X	X	X					X
272	X	X	X	X	X	X	X	X					X
273		X	X		X	X	X	X			X	X	X
274		X				X							X
275	X	X	X	X	X	X	X	X			X		X
276		X	X		X	X	X	X			X	X	X
277			X		X	X	X	X			X	X	
278		X	X		X	X	X	X			X	X	X
279		X	X		X		X	X			X	X	X
280	X	X	X	X	X	X	X	X					X
281	X	X	X		X	X	X	X					X
282	X	X	X	X	X	X	X	X			X	X	X
283	X	X	X	X	X	X		X					X
284	X		X	X	X	X		X			X		X
285	X	X	X	X	X	X							X
286	X	X	X		X	X	X	X					X
287		X		X	X		X						
288	X	X	X	X	X		X						X
289	X	X	X	X	X	X	X						X
290	X	X	X	X	X	X	X						X
291	X		X	X	X	X		X					X
292	X	X	X	X	X		X	X					X
293	X	X	X	X	X		X	X					X
294	X	X	X	X	X		X	X					X
295	X	X	X	X	X	X	X	X					X
296	X	X	X	X	X	X	X	X			X		
297	X	X	X	X	X	X	X	X			X	X	
298	X	X	X	X	X	X	X	X			X		X
299	X	X		X	X		X	X					

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23
300	X	X	X	X	X	X		
301	X	X	X	X	X	X		X
302	X	X	X					X
303					X			X
304	X	X	X	X	X	X	X	X
305	X	X	X					
306	X	X		X	X			X
307	X	X	X	X	X			
308	X	X	X					
309	X			X	X	X		X
310	X	X	X	X	X	X	X	X
311	X	X	X	X	X			X
312	X	X	X					X
313	X				X			X
314		X	X					
315								
316	X	X	X	X	X	X		X
317	X			X	X	X		X
318	X	X	X	X	X			X
319	X	X		X				X
320	X	X	X	X	X			X
321	X	X	X	X	X	X	X	X
322	X	X	X	X	X	X	X	X
323	X	X	X	X	X	X	X	X
324	X	X	X			X		X
325					X			X
326	X				X			X
327		X	X		X			
328								
330								
331								
332								
333								
334			X	X	X	X		
335								
336				X		X		
337			X		X	X		
338			X	X	X	X		

TABLE 3a - Continued

R2 \ R1	20	22	27	38	39	40	41	42	31	32	34	35	36	37
300		X		X	X	X	X	X	X	X		X	X	X
301		X		X	X	X	X		X	X	X	X	X	X
302										X	X		X	
303											X			X
304		X		X	X	X	X	X	X	X	X	X	X	X
305		X				X	X	X	X	X		X	X	X
306		X		X	X	X	X	X	X	X	X	X	X	
307		X		X		X	X		X	X		X	X	
308		X		X	X	X	X	X	X	X	X	X	X	X
309		X		X	X	X	X	X	X		X	X	X	
310		X		X	X	X	X	X	X	X	X	X	X	X
311				X	X	X	X	X	X			X	X	
312				X	X	X	X	X	X		X	X	X	
313				X	X	X		X			X	X	X	
314						X	X	X	X		X	X	X	
315														
316		X		X	X	X	X	X	X	X	X	X	X	X
317				X	X	X	X		X		X		X	
318		X		X			X		X			X	X	
319		X		X		X	X		X	X	X	X	X	X
320		X		X	X		X		X	X	X	X	X	X
321		X		X	X	X	X	X	X	X	X	X	X	
322		X		X	X	X	X		X	X	X	X	X	X
323		X		X		X	X	X	X	X	X	X	X	X
324							X							
325														
326		X									X			
327										X			X	
328		X					X			X				
330				X	X	X		X	X	X	X	X	X	X
331		X			X		X		X	X	X		X	X
332					X		X		X	X	X		X	X
333		X			X		X		X	X	X		X	X
334					X	X		X	X		X			
335					X	X			X					
336						X		X	X					
337					X	X		X	X					
338					X	X		X	X					

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	26	28	29	30
300	X	X	X		X	X	X	X					X
301		X	X		X	X	X				X		
302		X			X	X		X					
303					X								
304	X	X	X		X	X	X	X					X
305		X			X	X	X	X					X
306	X	X	X	X	X	X	X						X
307		X			X	X	X						
308		X		X	X	X	X	X					X
309	X	X	X	X	X		X					X	X
310	X	X	X	X	X		X	X			X		X
311	X	X			X	X	X						X
312	X				X	X							X
313	X	X			X		X	X					X
314	X					X							X
315	X												
316	X	X	X		X		X	X				X	X
317	X	X	X	X	X						X	X	X
318		X		X	X	X	X						X
319	X		X	X	X		X						X
320	X	X	X	X	X		X	X					X
321	X	X	X	X	X	X	X	X			X	X	X
322	X	X	X	X	X	X	X	X			X	X	X
323	X	X	X		X	X	X	X			X		X
324	X		X					X				X	
325	X		X										
326	X	X	X	X			X						X
327		X	X	X	X	X		X					X
328							X	X					X
330													X
331								X	X				
332								X	X				
333								X	X				
334												X	X
335													X
336													X
337													X
338													X

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23
339			X	X	X	X		
340			X	X		X		
341			X	X	X	X		
342			X	X	X	X		
343								
344				X		X		
345			X					
346				X	X	X		
347			X	X	X	X		
348			X	X	X	X		
349				X				
350				X	X	X		
351				X	X	X		
352			X	X		X		
353								
354								
355			X	X		X		
356			X	X	X	X		
357				X				
358			X					
359			X	X	X	X		
360			X	X		X		
361				X	X	X		
362				X	X	X		
363								
364			X					
365			X	X	X	X		
366			X	X				
367				X	X	X		
368								
369			X	X	X			
370			X	X	X			
371			X	X	X			
372			X					
373			X	X	X			
374			X					
375			X	X	X			
376			X		X			
377			X					

TABLE 3a - Continued

R2 \ R1	20	22	27	38	39	40	41	42	31	32	34	35	36	37
339					X	X		X	X		X			
340					X	X		X	X		X	X		
341					X			X	X		X			
342					X	X		X	X		X			
343						X		X	X			X		
344					X	X			X		X	X		
345					X	X		X	X		X			
346					X	X		X	X		X	X		
347					X	X		X	X		X	X		
348					X			X	X					
349					X	X			X		X	X		
350					X	X		X	X		X			
351					X	X			X		X			
352					X	X		X	X		X	X		
353						X								
354						X		X						
355					X	X		X	X		X	X		
356					X	X		X	X		X	X		
357								X						
358					X	X		X	X					
359					X	X		X	X		X	X		
360									X					
361					X	X		X	X		X			
362					X	X			X		X			
363					X				X					
364														
365											X			
366											X			
367											X			
368								X						
369					X				X		X	X		
370					X				X		X	X		
371					X				X		X	X		
372					X				X		X	X		
373					X				X		X	X		
374					X				X		X	X		
375					X				X		X	X		
376					X							X		
377					X				X		X	X		

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	26	28	29	30
339													X
340												X	X
341													X
342												X	X
343													X
344													
345													X
346													X
347													X
348													X
349													X
350													X
351												X	X
352												X	X
353													X
354													
355												X	X
356													X
357													X
358													X
359												X	X
360													X
361												X	X
362												X	X
363													X
364													
365												X	X
366													
367												X	X
368													
369													
370													
371													
372													
373													
374													
375													
376													
377													

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23
378				X	X			
379				X	X			
380				X	X			
381								
382								
383								
177	X		X		X	X	X	X
178	X		X	X	X	X	X	X
179	X		X	X	X	X	X	X
264								
189	X		X	X	X	X	X	X
198	X		X	X	X	X	X	X
200	X		X			X		X
202	X		X	X	X	X		X
217	X		X	X	X	X	X	X
218	X		X	X	X	X	X	X
219	X		X	X	X	X	X	X
223	X		X	X	X	X	X	X
224	X		X	X	X	X	X	X
225	X		X	X	X	X	X	X
226	X		X	X	X	X	X	X
227	X		X	X	X	X	X	X
230	X		X	X	X	X	X	X
242	X		X	X	X	X	X	X
245	X		X	X	X	X	X	X
248	X		X	X	X	X	X	X
251	X		X	X	X	X	X	X
258	X		X	X	X	X	X	X
260	X		X	X	X	X	X	X
329								
263								
236	X		X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1	20	22	27	38	39	40	41	42	31	32	34	35	36	37
378					X				X		X	X		
379					X				X		X	X		
380									X			X		
381									X			X		
382												X		
383									X		X	X		
177	X	X			X	X	X	X	X	X	X		X	X
178	X	X					X		X	X	X		X	X
179	X	X					X		X	X	X			X
264			X	X	X	X		X	X	X	X	X	X	X
189		X			X	X	X	X	X	X	X		X	X
198		X			X	X	X	X	X	X	X		X	X
200		X			X	X	X	X	X	X	X		X	X
202		X			X	X	X	X	X	X	X		X	X
217		X			X	X	X	X	X	X	X		X	X
218		X			X	X	X	X	X	X	X		X	X
219		X			X	X	X	X	X	X	X		X	X
223		X			X	X	X	X	X	X	X		X	X
224		X			X	X	X	X	X	X	X		X	X
225		X			X	X	X	X	X	X	X		X	X
226		X			X	X	X	X	X	X	X		X	X
227		X			X	X	X	X	X	X	X		X	X
230		X			X	X	X	X	X	X	X		X	X
242		X			X	X	X	X	X	X	X		X	X
245		X			X	X	X	X	X	X	X		X	X
248		X			X	X	X	X	X	X	X		X	X
251		X			X	X	X	X	X	X	X		X	X
258		X			X	X	X	X	X	X	X		X	X
260		X			X	X	X	X	X	X	X		X	X
329				X	X	X	X	X	X	X	X	X	X	X
263			X											
236					X	X	X	X	X	X	X		X	X

TABLE 3a - Continued

R2 \ R1	30	44	45	47	49	50	51	52
378								
379								
380								
381								
382								
383								
177								
178								
179								
264	X							
189		X	X	X			X	
198		X	X	X	X	X	X	X
200		X	X	X	X	X	X	X
202		X	X	X	X	X	X	X
217		X	X	X			X	
218		X	X	X			X	
219		X	X	X			X	
223		X	X	X			X	
224		X	X	X			X	
225		X	X	X	X	X	X	X
226		X	X	X	X	X	X	X
227		X	X	X		X	X	X
230		X	X	X	X	X	X	X
242		X	X	X	X	X	X	X
245		X	X	X	X		X	X
248		X	X	X	X	X	X	X
251		X	X	X	X	X	X	X
258		X	X	X	X	X	X	X
260		X	X	X	X	X	X	X
329	X		X	X	X	X	X	X
263		X	X	X	X	X	X	X
236		X		X			X	

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	26	28	29
378												
379												
380												
381												
382												
383												
177			X		X		X	X	X			
178	X		X		X	X	X	X	X	X		
179	X		X		X	X	X	X		X		
264												
189	X		X		X	X	X	X	X	X		
198	X		X		X	X	X	X	X	X		
200						X		X				
202	X		X		X	X	X		X	X		
217	X		X		X		X	X	X	X		
218	X		X		X	X	X	X	X	X		
219	X		X		X	X			X	X		
223	X				X	X	X	X	X	X		
224	X		X		X	X	X	X	X	X		
225	X		X		X	X	X	X	X	X		
226	X		X		X	X	X	X	X	X		
227	X				X	X	X	X	X	X		
230	X		X		X	X	X	X	X	X		
242	X		X		X	X	X	X	X	X		
245	X		X		X	X	X	X	X	X		
248	X		X		X	X	X	X	X	X		
251	X		X		X	X	X	X	X	X		
258	X		X		X	X	X	X	X	X		
260	X		X		X	X	X	X	X	X		
329												
263												
236			X		X	X	X	X		X		

TABLE 3a - Continued

R2 \ R1		2		9	10	11		14	15	23	22	39	40	41	42
180		X		X	X			X	X	X	X	X	X	X	X
181		X		X	X	X		X	X	X	X	X	X	X	X
182		X		X	X			X		X	X	X	X	X	X
183		X		X	X	X		X	X	X	X	X	X	X	X
184		X		X	X	X		X	X	X	X	X	X	X	X
185		X		X	X			X	X	X					
186		X		X				X		X		X	X	X	X
187		X		X	X	X		X	X	X	X	X	X	X	X
188		X		X	X	X		X	X	X	X	X	X	X	X
190		X		X		X		X	X	X	X	X	X	X	X
191		X		X		X		X	X	X	X	X	X	X	X
192		X		X	X	X		X	X	X	X	X	X	X	X
193		X		X		X		X	X	X	X	X	X	X	X
194		X		X	X	X		X	X	X	X	X	X	X	X
195		X		X	X	X		X	X	X	X	X	X	X	X
196		X		X	X	X		X	X	X	X	X	X	X	X
197		X		X	X	X		X	X	X	X	X	X	X	X
199		X		X	X	X		X	X	X	X	X	X	X	X
201		X		X	X	X		X		X	X			X	
203		X		X	X	X		X	X	X	X	X		X	
204		X		X	X	X		X	X	X	X	X	X	X	X
205		X		X	X	X		X	X	X	X	X	X	X	X
206		X		X	X	X		X		X	X	X	X	X	X
207		X		X	X	X		X	X	X	X	X	X	X	X
208		X		X	X	X		X	X	X	X	X	X	X	X
209		X		X	X	X		X		X	X			X	
210		X		X	X	X		X	X	X	X			X	
211		X		X	X	X		X	X	X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1	31	32	34	36	37		7	13	19	21	25	33	43	26
180	X	X	X	X	X			X	X	X		X	X	X
181	X	X	X	X	X		X	X	X	X	X		X	X
182		X	X	X	X		X	X				X	X	X
183	X	X	X	X	X		X	X	X	X	X	X	X	X
184	X	X	X				X	X	X	X		X	X	
185								X		X				
186	X	X	X									X		
187	X	X	X	X	X		X	X	X	X	X	X	X	X
188	X	X	X	X	X		X	X	X	X	X		X	X
190	X	X	X	X	X		X		X		X	X	X	X
191	X	X	X	X	X		X	X	X	X	X	X	X	X
192	X	X	X	X	X		X	X	X	X	X	X	X	
193	X	X	X	X	X		X	X	X	X	X	X	X	X
194	X	X	X	X	X		X	X	X	X	X	X	X	X
195	X	X	X	X	X		X	X	X	X	X	X	X	
196	X	X	X	X	X		X	X	X	X	X		X	
197	X	X	X	X	X		X	X	X	X	X	X	X	X
199	X	X	X	X	X		X	X	X	X	X	X	X	X
201	X	X	X	X	X		X	X	X	X	X	X	X	X
203	X	X	X	X	X		X	X	X	X	X	X		X
204	X	X	X	X	X		X	X	X	X	X	X	X	X
205	X	X	X	X	X		X	X	X	X	X		X	X
206	X	X	X	X	X		X	X	X	X	X	X	X	X
207	X	X	X	X	X		X	X	X	X	X		X	X
208	X	X	X	X	X		X	X	X	X	X	X	X	X
209	X	X	X				X	X	X	X	X	X		X
210	X	X	X	X	X		X		X	X	X	X		X
211	X	X	X	X	X		X	X	X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1		2		9	10	11		14	15	23	22	39	40	41	42
212		X		X	X	X		X	X	X	X	X	X	X	X
213		X		X	X	X		X		X	X			X	
214		X		X	X	X		X	X	X	X	X		X	X
215		X		X				X	X	X					
216		X		X	X	X		X	X	X	X	X	X	X	X
220		X		X	X	X		X	X	X	X	X	X	X	X
221		X		X	X	X		X	X	X	X	X	X	X	X
222		X		X				X	X	X	X	X	X	X	X
228		X		X	X	X		X	X	X	X	X	X	X	X
229		X		X	X	X		X	X	X					
231		X		X	X	X		X	X	X		X	X	X	X
232		X		X	X	X		X	X	X	X	X	X	X	X
233		X		X	X	X		X	X	X	X	X	X	X	X
234		X		X	X	X		X	X	X	X	X	X	X	X
235		X		X	X	X		X	X	X		X	X	X	X
237		X		X	X	X		X	X	X	X			X	
238		X		X	X	X		X	X	X	X	X	X	X	X
239		X		X	X	X		X	X	X		X	X	X	X
240		X		X	X	X		X	X	X	X	X	X	X	X
241		X		X	X	X		X	X	X	X	X	X	X	X
243		X		X	X	X		X	X	X	X	X	X	X	X
244		X		X	X	X		X	X	X	X	X	X	X	X
246		X		X	X	X		X	X	X	X	X	X	X	
247		X		X	X	X		X	X	X	X	X	X	X	
249		X		X	X	X		X	X	X	X	X	X	X	X
250		X		X	X	X		X	X	X	X	X	X	X	X
252		X		X	X	X		X	X	X	X	X	X	X	X
253		X		X	X	X		X	X	X				X	
254		X		X	X	X		X	X	X	X	X	X	X	X
255		X		X	X	X		X	X	X	X	X	X	X	X
256		X		X	X	X		X	X	X	X	X	X	X	X
257		X		X	X	X		X	X	X	X	X	X	X	X
259		X		X	X	X		X	X	X	X	X		X	
261		X		X	X	X		X	X	X	X	X	X	X	X
262		X		X	X	X		X	X	X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1	31	32	34	36	37		7	13	19	21	25	33	43	26
212	X	X	X				X	X	X	X	X	X	X	X
213	X	X	X		X		X	X	X	X	X	X	X	X
214	X	X	X	X			X	X	X	X	X	X	X	X
215														X
216	X	X	X	X			X	X	X	X	X	X	X	X
220	X	X	X	X	X		X	X		X	X	X	X	X
221	X	X	X	X	X		X	X	X	X	X		X	X
222	X	X	X	X	X					X	X	X	X	X
228	X	X	X	X	X		X	X	X	X	X	X	X	X
229							X	X	X	X	X			X
231	X	X	X	X	X		X	X			X	X		X
232	X	X	X	X	X		X	X	X	X	X		X	X
233	X	X	X	X	X		X	X	X		X	X	X	X
234		X	X	X	X		X	X	X	X	X		X	X
235	X	X	X	X	X		X	X	X	X	X	X		X
237	X	X	X	X	X		X	X	X	X	X	X	X	X
238			X	X	X		X	X	X	X	X	X	X	X
239	X	X	X	X	X		X	X	X	X	X	X		X
240		X	X	X	X		X	X	X	X	X		X	X
241	X	X	X	X	X		X	X	X	X	X	X	X	X
243	X	X	X	X	X		X	X	X	X	X		X	X
244	X	X	X	X	X		X	X	X	X	X		X	X
246	X	X	X	X	X		X	X	X	X	X	X	X	X
247	X	X	X				X	X	X	X	X	X	X	X
249	X	X	X	X	X		X	X	X	X	X	X		X
250	X	X	X	X	X		X	X	X	X	X	X	X	X
252	X	X	X	X	X		X	X	X	X	X	X	X	X
253	X	X	X				X	X	X	X	X	X	X	X
254	X	X	X	X	X		X	X	X	X	X	X	X	X
255	X	X	X	X	X		X	X	X	X	X	X	X	X
256	X	X	X	X	X		X	X	X	X	X	X	X	X
257	X	X	X	X	X		X	X	X	X	X	X		X
259	X	X	X	X	X		X	X	X	X	X	X	X	X
261	X	X	X	X	X		X	X	X	X	X	X	X	X
262	X	X	X	X	X		X	X	X	X	X	X		X

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23		22
265										
266	X	X	X	X	X	X	X	X		
267	X	X	X	X	X	X	X	X		X
268	X	X	X	X	X	X	X	X		X
269	X	X	X	X		X	X	X		X
270	X	X	X	X	X	X	X	X		X
271	X	X	X	X	X	X		X		X
272	X	X	X	X	X	X		X		X
273	X	X	X	X	X	X		X		X
274			X							X
275	X	X	X	X	X		X	X		X
276	X	X	X	X	X	X		X		X
277	X	X		X	X	X	X	X		X
278	X	X	X	X	X	X	X	X		X
279	X	X	X	X	X	X	X	X		X
280	X	X	X	X	X	X		X		X
281	X	X	X	X	X	X		X		X
282	X	X	X	X	X	X	X	X		X
283	X	X	X	X	X	X		X		X
284	X	X	X	X	X	X	X	X		X
285	X	X	X	X	X	X		X		X
286	X	X	X		X					X
287	X	X		X	X			X		X
288	X	X	X	X	X	X		X		X
289	X	X	X	X	X			X		X
290	X	X	X	X	X			X		X
291	X	X	X	X				X		X
292	X	X	X	X	X	X		X		X
293	X	X	X	X	X	X		X		X
294	X	X	X		X			X		X
295	X	X	X	X	X	X	X	X		X
296	X	X	X	X	X	X		X		X
297	X	X	X	X	X	X	X	X		X
298	X	X	X	X	X		X	X		X
299	X	X						X		X
300	X	X	X	X	X	X				X
301	X	X	X	X	X	X		X		X

TABLE 3a - Continued

R2 \ R1	38	39	40	41	42	31	32	34	35	36	37	30
265												
266	X	X	X	X	X			X	X			X
267	X	X	X	X	X	X	X	X	X	X	X	X
268	X	X	X	X	X	X	X	X	X	X	X	X
269	X	X	X	X	X	X	X	X	X	X	X	X
270	X	X	X	X		X	X	X	X	X	X	X
271	X		X	X		X	X	X	X	X	X	X
272	X	X		X	X	X	X	X		X	X	X
273	X	X	X	X	X	X	X	X	X	X	X	X
274							X					X
275		X	X	X	X	X	X	X	X	X	X	X
276	X	X	X	X	X	X	X	X	X	X	X	X
277		X	X	X	X	X	X	X	X	X		
278		X	X	X	X	X	X	X	X	X	X	X
279	X	X	X	X	X	X	X	X	X	X	X	X
280		X	X	X	X	X		X	X	X		X
281	X	X	X	X	X	X	X	X	X	X	X	X
282	X	X	X	X	X	X	X	X	X	X	X	X
283	X		X	X	X	X	X	X	X	X	X	X
284	X	X	X	X	X	X	X	X	X	X	X	X
285	X	X		X	X		X		X	X	X	X
286					X		X	X		X	X	X
287	X		X	X	X	X			X	X		
288	X	X	X	X	X	X	X	X	X	X	X	X
289	X	X	X	X	X	X		X	X	X	X	X
290	X	X	X		X	X	X	X		X		X
291	X	X	X		X	X	X	X	X	X		X
292	X	X	X	X	X	X	X	X	X	X		X
293	X	X	X	X	X	X	X	X	X	X	X	X
294	X	X	X	X		X	X	X	X	X	X	X
295	X	X	X		X	X	X	X	X	X	X	X
296	X	X	X	X	X	X	X	X	X	X		
297	X	X	X	X	X	X	X	X	X	X	X	
298	X	X	X	X	X	X	X	X	X	X	X	X
299				X	X		X					
300	X	X	X	X	X	X	X		X	X	X	X
301	X	X	X	X		X	X	X	X	X	X	

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	28	29
265											
266		X	X	X		X				X	
267	X	X	X	X	X	X	X	X		X	X
268	X	X	X	X	X	X	X	X		X	X
269	X	X	X		X	X		X		X	X
270	X	X	X		X	X	X	X		X	X
271	X	X	X	X	X	X	X	X			
272	X	X	X	X	X	X	X	X			
273		X	X		X	X	X	X		X	X
274		X				X					
275	X	X	X	X	X	X	X	X		X	
276		X	X		X	X	X	X		X	X
277			X		X	X	X	X		X	X
278		X	X		X	X	X	X		X	X
279		X	X		X		X	X		X	X
280	X	X	X	X	X	X	X	X			
281	X	X	X		X	X	X	X			
282	X	X	X	X	X	X	X	X		X	X
283	X	X	X	X	X	X		X			
284	X		X	X	X	X		X		X	
285	X	X	X	X	X	X					
286	X	X	X		X	X	X	X			
287		X		X	X		X				
288	X	X	X	X	X		X				
289	X	X	X	X	X	X	X				
290	X	X	X	X	X	X	X				
291	X		X	X	X	X		X			
292	X	X	X	X	X		X	X			
293	X	X	X	X	X		X	X			
294	X	X	X	X	X		X	X			
295	X	X	X	X	X	X	X	X			
296	X	X	X	X	X	X	X	X		X	
297	X	X	X	X	X	X	X	X		X	X
298	X	X	X	X	X	X	X	X		X	
299	X	X		X	X		X	X			
300	X	X	X		X	X	X	X			
301		X	X		X	X	X			X	

TABLE 3a - Continued

R2 \ R1	2	3	9	10	11	14	15	23		22
302	X	X	X					X		
303					X			X		
304	X	X	X	X	X	X	X	X		X
305	X	X	X							X
306	X	X		X	X			X		X
307	X	X	X	X	X					X
308	X	X	X							X
309	X			X	X	X		X		X
310	X	X	X	X	X	X	X	X		X
311	X	X	X	X	X			X		
312	X	X	X					X		
313	X				X			X		
314		X	X							
315										
316	X	X	X	X	X	X		X		X
317	X			X	X	X		X		
318	X	X	X	X	X			X		X
319	X	X		X				X		X
320	X	X	X	X	X			X		X
321	X	X	X	X	X	X	X	X		X
322	X	X	X	X	X	X	X	X		X
323	X	X	X	X	X	X	X	X		X
324	X	X	X			X		X		
325					X			X		
326	X				X			X		X
327		X	X		X					
328										X
330										
331										X
332										
333										X
334			X	X	X	X				

TABLE 3a - Continued

R2 \ R1	38	39	40	41	42	31	32	34	35	36	37	30
302							X	X		X		
303								X			X	
304	X	X	X	X	X	X	X	X	X	X	X	X
305			X	X	X	X	X		X	X	X	X
306	X	X	X	X	X	X	X	X	X	X		X
307	X		X	X		X	X		X	X		
308	X	X	X	X	X	X	X	X	X	X	X	X
309	X	X	X	X	X	X		X	X	X		X
310	X	X	X	X	X	X	X	X	X	X	X	X
311	X	X	X	X	X	X			X	X		X
312	X	X	X	X	X	X		X	X	X		X
313	X	X	X		X			X	X	X		X
314			X	X	X	X		X	X	X		X
315												
316	X	X	X	X	X	X	X	X	X	X	X	X
317	X	X	X	X		X		X		X		X
318	X			X		X			X	X		X
319	X		X	X		X	X	X	X	X	X	X
320	X	X		X		X	X	X	X	X	X	X
321	X	X	X	X	X	X	X	X	X	X		X
322	X	X	X	X		X	X	X	X	X	X	X
323	X		X	X	X	X	X	X	X	X	X	X
324				X								
325												
326								X				X
327							X			X		X
328				X			X					X
330	X	X	X		X	X	X	X	X	X	X	X
331		X		X		X	X	X		X	X	
332		X		X		X	X	X		X	X	
333		X		X		X	X	X		X	X	
334		X	X		X	X		X				X

TABLE 3a - Continued

R2 \ R1	7	8	13	17	19	21	25	33	43	28	29
302		X			X	X		X			
303					X						
304	X	X	X		X	X	X	X			
305		X			X	X	X	X			
306	X	X	X	X	X	X	X				
307		X			X	X	X				
308		X		X	X	X	X	X			
309	X	X	X	X	X		X				X
310	X	X	X	X	X		X	X		X	
311	X	X			X	X	X				
312	X				X	X					
313	X	X			X		X	X			
314	X					X					
315	X										
316	X	X	X		X		X	X			X
317	X	X	X	X	X					X	X
318		X		X	X	X	X				
319	X		X	X	X		X				
320	X	X	X	X	X		X	X			
321	X	X	X	X	X	X	X	X		X	X
322	X	X	X	X	X	X	X	X		X	X
323	X	X	X		X	X	X	X		X	
324	X		X					X			X
325	X		X								
326	X	X	X	X			X				
327		X	X	X	X	X		X			
328							X	X			
330											
331								X	X		
332								X	X		
333								X	X		
334											X

TABLE 3a - Continued

R2 \ R1		9	10	11	14	39
335						X
336			X		X	
337		X		X	X	X
338		X	X	X	X	X
339		X	X	X	X	X
340		X	X		X	X
341		X	X	X	X	X
342		X	X	X	X	X
343						
344			X		X	X
345		X				X
346			X	X	X	X
347		X	X	X	X	X
348		X	X	X	X	X
349			X			X
350			X	X	X	X
351			X	X	X	X
352		X	X		X	X
353						
354						
355		X	X		X	X
356		X	X	X	X	X
357			X			
358		X				X

TABLE 3a - Continued

R2 \ R1	40	42	31	34	35		30	29
335	X		X				X	
336	X	X	X				X	
337	X	X	X				X	
338	X	X	X				X	
339	X	X	X	X			X	
340	X	X	X	X	X		X	X
341		X	X	X			X	
342	X	X	X	X			X	X
343	X	X	X		X		X	
344	X		X	X	X			
345	X	X	X	X			X	
346	X	X	X	X	X		X	
347	X	X	X	X	X		X	
348		X	X				X	
349	X		X	X	X		X	
350	X	X	X	X			X	
351	X		X	X			X	X
352	X	X	X	X	X		X	X
353	X						X	
354	X	X						
355	X	X	X	X	X		X	X
356	X	X	X	X	X		X	
357		X					X	
358	X	X	X				X	

TABLE 3a - Continued

R2 \ R1		9	10	11	14	39
359		X	X	X	X	X
360		X	X		X	
361			X	X	X	X
362			X	X	X	X
363						X
364		X				
365		X	X	X	X	
366		X	X			
367			X	X	X	
368						
369		X	X	X		X
370		X	X	X		X
371		X	X	X		X
372		X				X
373		X	X	X		X
374		X				X
375		X	X	X		X
376		X		X		X
377		X				X
378			X	X		X
379			X	X		X
380			X	X		
381						
382						
383						

TABLE 3a - Continued

R2 \ R1	40	42	31	34	35		30	29
359	X	X	X	X	X		X	X
360			X				X	
361	X	X	X	X			X	X
362	X		X	X			X	X
363			X				X	
364								
365				X			X	X
366				X				
367				X			X	X
368		X						
369			X	X	X			
370			X	X	X			
371			X	X	X			
372			X	X	X			
373			X	X	X			
374			X	X	X			
375			X	X	X			
376					X			
377			X	X	X			
378			X	X	X			
379			X	X	X			
380			X		X			
381			X		X			
382					X			
383			X	X	X			

TABLE 3a - Continued

R2 \ R1	2	9	10	11	14	15	23	20
177	X	X		X	X	X	X	X
178	X	X	X	X	X	X	X	X
179	X	X	X	X	X	X	X	X
264								
189	X	X	X	X	X	X	X	
198	X	X	X	X	X	X	X	
200	X	X			X		X	
202	X	X	X	X	X		X	
217	X	X	X	X	X	X	X	
218	X	X	X	X	X	X	X	
219	X	X	X	X	X	X	X	
223	X	X	X	X	X	X	X	
224	X	X	X	X	X	X	X	
225	X	X	X	X	X	X	X	
226	X	X	X	X	X	X	X	
227	X	X	X	X	X	X	X	
230	X	X	X	X	X	X	X	
242	X	X	X	X	X	X	X	
245	X	X	X	X	X	X	X	
248	X	X	X	X	X	X	X	
251	X	X	X	X	X	X	X	
258	X	X	X	X	X	X	X	
260	X	X	X	X	X	X	X	
329								
263								
236	X	X	X	X	X	X	X	

TABLE 3a - Continued

R2 \ R1	22	27	38	39	40	41	42	31	32	34	35	36	37	30
177	X			X	X	X	X	X	X	X		X	X	
178	X					X		X	X	X		X	X	
179	X					X		X	X	X			X	
264		X	X	X	X		X	X	X	X	X	X	X	X
189	X			X	X	X	X	X	X	X		X	X	
198	X			X	X	X	X	X	X	X		X	X	
200	X			X	X	X	X	X	X	X		X	X	
202	X			X	X	X	X	X	X	X		X	X	
217	X			X	X	X	X	X	X	X		X	X	
218	X			X	X	X	X	X	X	X		X	X	
219	X			X	X	X	X	X	X	X		X	X	
223	X			X	X	X	X	X	X	X		X	X	
224	X			X	X	X	X	X	X	X		X	X	
225	X			X	X	X	X	X	X	X		X	X	
226	X			X	X	X	X	X	X	X		X	X	
227	X			X	X	X	X	X	X	X		X	X	
230	X			X	X	X	X	X	X	X		X	X	
242	X			X	X	X	X	X	X	X		X	X	
245	X			X	X	X	X	X	X	X		X	X	
248	X			X	X	X	X	X	X	X		X	X	
251	X			X	X	X	X	X	X	X		X	X	
258	X			X	X	X	X	X	X	X		X	X	
260	X			X	X	X	X	X	X	X		X	X	
329			X	X	X	X	X	X	X	X	X	X	X	X
263		X												
236				X	X	X	X	X	X	X		X	X	

TABLE 3a - Continued

R2 \ R1	44	45	47	49	50	51	52	7	13	19	21	25	33	43	26
177									X	X		X	X	X	
178								X	X	X	X	X	X	X	X
179								X	X	X	X	X	X		X
264															
189	X	X	X			X		X	X	X	X	X	X	X	X
198	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
200	X	X	X	X	X	X	X				X		X		
202	X	X	X	X	X	X	X	X	X	X	X	X		X	X
217	X	X	X			X		X	X	X		X	X	X	X
218	X	X	X			X		X	X	X	X	X	X	X	X
219	X	X	X			X		X	X	X	X			X	X
223	X	X	X			X		X		X	X	X	X	X	X
224	X	X	X			X		X	X	X	X	X	X	X	X
225	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
226	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
227	X	X	X		X	X	X	X		X	X	X	X	X	X
230	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
242	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
245	X	X	X	X		X	X	X	X	X	X	X	X	X	X
248	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
251	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
258	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
260	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
329		X	X	X	X	X	X								
263	X	X	X	X	X	X	X								
236	X		X			X			X	X	X	X	X		X

TABLE 3a - Continued

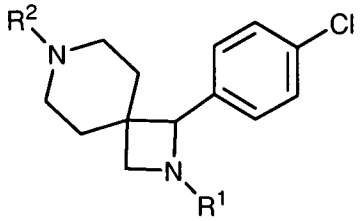
R2 \ R1	22	44	45	47	49	50	51	52
384		X	X	X	X	X	X	X
385		X	X	X	X	X	X	X
386		X	X	X	X	X	X	X
387		X	X	X	X	X	X	X
388		X	X	X	X	X	X	X
389		X	X	X	X	X	X	X
390		X	X	X	X	X	X	X
391		X	X	X	X	X	X	X
392		X	X	X	X	X	X	X
393		X	X	X	X	X	X	X
394		X	X	X	X		X	X
395		X	X	X	X	X	X	X
396		X	X	X	X	X	X	X
397		X	X	X	X	X	X	X
398		X	X	X	X	X	X	X
399		X	X	X	X	X	X	X
400		X	X	X	X	X	X	X
401		X	X	X	X	X	X	X
402		X	X	X	X	X	X	X
403		X	X	X	X	X	X	X
404		X	X	X	X	X	X	X
405		X	X	X	X	X	X	X
406		X	X	X	X	X	X	X
407		X	X	X	X	X	X	X
408		X	X	X	X	X	X	X
409		X	X	X	X	X	X	X
410		X	X	X	X	X	X	X
411		X	X	X	X	X	X	X
412		X	X	X	X	X	X	X
413		X	X	X	X	X	X	X
414		X	X	X	X	X	X	X
415		X	X	X	X	X	X	X
416		X	X	X	X	X	X	X
417		X	X	X	X	X	X	X
418		X		X		X	X	X
419		X	X	X	X	X	X	X
420		X		X	X	X	X	X
421		X	X	X	X	X	X	X
422		X	X	X	X	X	X	X
423		X	X	X	X	X	X	X

TABLE 3a - Continued

R2 \ R1	22	44	45	47	49	50	51	52
424		X	X	X	X	X	X	X
425		X	X	X	X	X	X	X
426		X	X	X	X	X	X	X
427		X	X	X	X	X	X	X
428		X	X	X	X	X	X	X
429		X	X	X	X	X	X	X
430		X	X	X	X	X	X	X
431		X	X	X	X	X	X	X
432		X	X	X	X	X	X	X
434			X	X	X	X	X	X
437			X	X	X	X	X	X
433				X			X	X
435				X			X	X
436				X			X	X
438				X			X	X

Table 3b

Table 3b is directed to compounds of the formula (IB):



(IB)

wherein R^1 and R^2 are as defined in Table 3b.

An "X" in the box formed by the intersection of the R^2 and the R^1 row represents an R^2 and R^1 combination of a compound of formula IB that is included in the definition of the compounds of formula I useful in the methods of this invention. For example, compounds of formula IB wherein R^2 is moiety 3 (see Table 2 for definition) and R^1 is moiety 45 (see Table 1 for definition) are included in the definition of formula I (there is an "X" in the box formed by the intersection of the R^2 column and the R^1 row).

If there is no "X" in the box, then that compound is not within the definition of the compounds of formula I. For example, compounds of formula IB wherein moiety R^2 is 3 and moiety R^1 is 44 (no "X" in the box formed by the intersection of the R^2 column and the R^1 row) are not within the definition of the compounds of formula I.

Table 3b

R2 \ R1	45	46	47	48	49	50	51	52	44
3	X	X	X	X	X	X	X	X	
5	X	X	X	X	X	X	X	X	
16	X	X	X	X		X	X	X	
20	X	X	X	X	X	X	X	X	
22	X	X	X	X	X	X	X	X	
30	X	X	X	X	X	X	X	X	
35	X	X	X		X	X	X	X	
44	X	X	X	X		X	X	X	
47	X	X	X	X	X	X	X	X	
48	X	X	X	X	X	X	X	X	
55	X	X	X	X	X	X	X	X	
59	X	X	X	X	X	X	X	X	
60	X	X	X	X	X	X	X	X	
64	X	X	X	X	X	X	X	X	
68	X	X	X	X	X	X	X	X	
83	X	X	X		X	X	X	X	
84	X	X	X	X	X	X	X	X	
85	X	X	X	X	X	X	X	X	
133					X	X	X		
134	X	X	X	X	X	X	X	X	
135	X	X	X	X	X	X	X	X	
136	X	X	X	X	X	X	X	X	
138	X	X	X	X	X	X	X	X	
139	X	X	X	X	X	X	X	X	
140	X	X	X	X	X	X	X	X	
141	X	X		X	X	X	X	X	
144	X	X	X	X	X	X	X	X	
146	X	X	X	X	X	X	X	X	
152	X	X	X	X	X	X	X	X	
157	X	X	X	X	X		X	X	
167	X	X	X	X	X	X	X	X	
175	X	X	X	X	X	X	X	X	
189	X	X	X		X	X	X	X	X
198	X	X	X	X	X	X	X	X	
200	X	X	X	X	X	X	X	X	
202	X	X	X	X	X	X	X	X	
217	X	X	X		X	X	X	X	X
218	X	X	X		X	X	X	X	X

Table 3b - Continued

R2 \ R1	45	46	47	48	49	50	51	52	44
219	X	X	X		X	X	X	X	
223	X	X	X		X	X	X	X	X
224	X	X	X		X	X	X	X	X
225	X	X	X	X	X	X	X	X	
226	X	X	X	X	X	X	X	X	
227	X	X	X	X	X	X	X	X	
230	X	X	X	X	X	X	X	X	
236	X	X	X		X	X	X	X	
242	X	X	X	X	X	X	X	X	
245	X		X	X	X	X	X	X	
248	X	X	X	X		X	X	X	
251	X	X	X	X	X	X	X	X	
258	X	X	X	X	X	X	X	X	
260	X	X	X	X	X	X	X	X	
263	X	X	X	X	X	X	X	X	
329	X	X	X	X	X	X	X	X	
384	X	X	X	X	X	X	X	X	
385	X	X	X	X	X	X	X	X	
386	X	X	X	X	X	X	X	X	
387	X	X	X		X	X	X	X	
388	X	X	X	X	X	X	X	X	
389	X	X	X	X		X	X	X	
390	X	X	X	X	X	X	X	X	
391	X	X	X	X	X	X	X	X	
392	X	X	X	X	X	X	X	X	
393	X	X	X	X	X	X	X	X	
394	X		X	X	X	X	X	X	
395	X	X	X	X	X	X	X	X	
396	X	X	X	X	X	X	X	X	
397	X	X	X	X	X	X	X	X	
398	X	X	X	X	X	X	X	X	
399	X	X	X	X	X	X	X	X	
400	X	X	X	X	X	X	X	X	
401	X	X	X	X	X	X	X	X	
402	X	X	X	X	X	X	X	X	
403	X		X	X	X	X	X	X	
404	X	X	X	X	X	X	X	X	
405	X	X	X	X	X	X	X	X	
406	X		X	X	X	X	X	X	
407	X	X	X	X	X	X	X	X	

Table 3b - Continued

R2 \ R1	45	46	47	48	49	50	51	52	44
408	X	X	X	X	X	X	X	X	
409	X	X	X	X	X	X	X	X	
410	X	X	X	X	X	X	X	X	
411	X	X	X	X	X	X	X	X	
412	X	X	X	X	X	X	X	X	
413	X	X	X	X	X	X	X	X	
414	X	X	X	X	X	X	X	X	
415	X	X	X	X	X	X	X	X	
416	X	X	X	X	X	X	X	X	
417	X	X	X	X	X	X	X	X	
418	X	X	X	X	X	X	X	X	
419	X	X	X	X	X	X	X	X	
420	X		X	X	X	X	X	X	
421	X	X	X	X	X	X	X	X	
422	X	X	X	X	X	X	X	X	
423	X	X	X	X	X	X	X	X	
424	X	X	X	X	X	X	X	X	
425	X	X	X	X		X	X	X	
426	X	X	X	X	X	X	X	X	
427	X	X	X	X	X	X	X	X	
428	X	X	X	X	X	X	X	X	
429	X	X	X	X	X	X	X	X	
430	X	X	X	X	X	X	X	X	
431	X	X	X	X	X	X	X	X	
432	X	X	X	X		X	X	X	
433	X		X		X	X	X	X	
434	X	X	X	X	X	X	X	X	
435	X	X	X		X	X	X	X	
436	X		X			X	X	X	
437	X	X	X		X	X	X	X	
438	X		X			X	X	X	
469	X	X	X	X	X	X	X	X	
470	X	X	X	X	X	X	X	X	
471	X	X	X	X	X	X	X	X	
472	X		X	X	X	X	X	X	
473	X	X	X	X	X		X	X	
474	X	X	X	X	X	X	X	X	
475	X		X		X		X	X	
476	X	X	X	X	X	X	X	X	

Table 3b - Continued

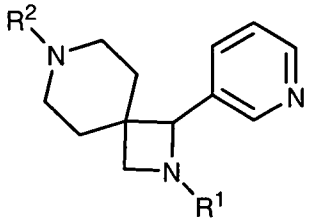
R2 \ R1	45	46	47	48	49	50	51	52	44
477	X	X	X	X	X	X	X	X	
478	X	X	X	X	X	X	X	X	
479	X	X	X	X	X	X	X	X	
480	X	X	X	X	X	X	X	X	
481	X	X	X	X	X	X	X	X	
482	X	X	X	X	X	X	X	X	
483	X	X	X	X	X	X	X	X	
484	X	X	X	X	X	X	X	X	
485	X	X		X	X	X	X	X	
486	X	X	X	X	X	X	X	X	
487	X	X	X	X	X	X	X	X	
488					X	X	X		
489	X	X	X	X	X	X	X	X	
490	X	X	X	X	X	X	X	X	
491	X	X	X	X	X	X	X	X	
492	X	X	X	X	X	X	X	X	
493		X	X	X	X	X	X		
494	X	X	X	X	X	X	X	X	
495	X	X	X	X	X	X	X		
496		X	X	X	X	X	X	X	
497	X	X	X	X	X	X	X	X	
498	X	X	X		X		X	X	
500	X	X	X		X	X	X	X	X
501	X	X	X		X	X	X	X	X
502	X	X	X		X	X	X	X	X
503	X	X	X		X	X	X	X	X
504	X	X	X		X	X	X	X	X
505	X	X	X		X		X	X	
506	X	X	X		X	X	X	X	X
507	X	X	X		X	X	X	X	X
508	X	X	X		X	X	X	X	X
509	X	X	X		X	X	X	X	X
510	X	X	X		X	X	X	X	X
511	X	X	X		X		X	X	X
512	X	X	X		X	X	X	X	X
513	X	X	X		X	X	X	X	X
514	X	X	X		X	X	X	X	X
515	X	X	X		X	X	X	X	X
516	X	X	X		X	X	X	X	X
517	X	X	X		X	X	X	X	X

Table 3b - Continued

R2 \ R1	45	46	47	48	49	50	51	52	44
518	X	X	X		X	X	X	X	
519	X	X	X		X	X	X	X	X
520	X	X	X		X	X	X	X	X
521		X	X		X	X	X	X	
522		X	X		X		X	X	
523	X	X	X		X			X	
524	X	X	X		X	X	X	X	
525	X	X	X		X	X	X	X	X
526	X	X	X		X	X	X	X	X
527	X	X	X		X	X	X	X	X
528	X	X	X		X	X	X	X	X
529	X	X	X			X	X	X	X
530	X	X	X		X	X	X	X	X
531	X	X	X		X	X		X	X
532	X	X	X		X	X		X	X
533	X	X	X		X	X		X	X
534	X	X	X		X		X	X	X
535		X	X		X		X	X	X
536		X	X		X		X	X	X

Table 3c

Table 3c is directed to compounds of the formula (IC):



(IC)

wherein R^1 and R^2 are as defined in Table 3c.

An "X" in the box formed by the intersection of the R^2 and the R^1 row represents an R^2 and R^1 combination of a compound of formula IC that is included in the definition of the compounds of formula I useful in the methods of this invention. For example, compounds of formula IC wherein R^2 is moiety 3 (see Table 2 for definition) and R^1 is moiety 44 (see Table 1 for definition) are included in the definition of formula I (there is an "X" in the box formed by the intersection of the R^2 column and the R^1 row).

If there is no "X" in the box, then that compound is excluded from the definition of the compounds of formula I. For example, compounds of formula IC wherein

moiety R^2 is 3 and moiety R^1 is 50 (no "X" in the box formed by the intersection of the R^2 column and the R^1 row) are excluded from the definition of the compounds of formula I.

5

Table 3c

R2 \ R1	44	46	47	51	50
3	X	X	X	X	
5	X	X	X	X	
16	X	X	X	X	
20	X	X	X	X	
22	X	X	X	X	
30	X	X	X	X	
35	X	X	X	X	
44	X	X	X	X	
47	X	X	X	X	
48	X	X	X	X	
55	X	X	X	X	
59	X	X	X	X	
60	X	X	X	X	
64	X	X	X	X	
68	X	X	X	X	
83	X			X	
84	X	X	X	X	
85	X	X		X	
133	X		X		
134	X	X	X	X	
135	X	X	X	X	
136	X	X	X	X	
138	X	X	X	X	
139	X	X	X	X	
140	X	X	X	X	
141	X	X	X	X	
144	X	X	X	X	
146	X	X	X	X	
152	X	X	X	X	
157	X	X	X	X	
167	X	X	X	X	
175	X	X	X	X	
189	X	X	X	X	X
198	X	X	X	X	
200	X	X	X	X	
202	X	X	X	X	
217	X	X	X	X	X
218	X	X	X	X	X
219	X	X	X	X	X
223	X	X	X	X	X

R2 \ R1	44	46	47	51	50
224	X	X	X	X	X
225	X	X	X	X	
226	X	X	X	X	
227	X	X	X	X	
230	X	X	X	X	
236	X	X	X	X	X
242	X	X	X	X	
245	X	X		X	
248	X	X	X	X	
251	X	X	X	X	
258	X	X	X	X	
260	X	X	X	X	
263	X	X	X	X	
329	X	X	X	X	
384	X	X	X	X	
385	X	X	X	X	
386	X	X	X	X	
387	X	X	X	X	
388	X	X	X	X	
389	X	X	X	X	
390	X	X	X	X	
391	X	X	X	X	
392	X	X	X	X	
393	X	X	X	X	
394	X		X	X	
395	X	X	X	X	
396	X	X	X	X	
397	X	X	X	X	
398	X	X	X	X	
399	X	X	X	X	
400	X	X	X	X	
401	X	X	X	X	
402	X	X	X	X	
403	X	X	X	X	
404	X	X	X	X	
405	X	X	X	X	
406	X	X	X	X	
407	X	X	X	X	
408	X	X	X	X	

Table 3c - Continued

R2 \ R1	44	46	47	51	50
409	X	X	X	X	
410	X	X	X	X	
411	X	X	X	X	
412	X	X	X	X	
413	X	X	X	X	
414	X		X	X	
415	X	X	X	X	
416	X	X	X	X	
417	X	X	X	X	
418	X			X	
419	X	X	X	X	
420	X	X	X	X	
421	X	X	X	X	
422	X	X	X	X	
423	X	X	X	X	
424	X	X	X	X	
425	X	X	X	X	
426	X	X	X	X	
427	X	X	X	X	
428	X	X	X	X	
429	X	X	X	X	
430	X	X	X	X	
431	X	X	X	X	
432	X	X	X	X	
433	X			X	
434	X	X	X	X	
435	X			X	
436	X			X	
437	X	X	X	X	
438	X			X	
469	X	X	X		
470	X	X	X	X	
471	X	X	X	X	
472	X	X	X	X	
473	X	X	X	X	
474	X	X	X	X	
475	X	X	X	X	
476	X	X		X	
477	X	X	X	X	

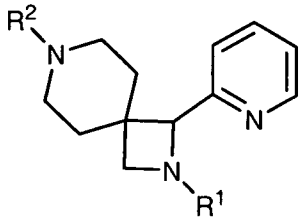
R2 \ R1	44	46	47	51	50
478	X	X	X	X	
479	X	X	X	X	
480	X	X	X	X	
481	X	X		X	
482	X	X	X	X	
483	X	X	X	X	
484	X	X	X	X	
485	X	X	X	X	
486	X	X	X	X	
487	X				
488	X				
489	X	X	X	X	
490	X	X	X	X	
491	X	X	X	X	
492	X	X	X	X	
493	X	X	X	X	
494	X	X	X	X	
495	X	X	X	X	
496		X	X	X	
497		X	X	X	
498		X	X	X	
500	X	X	X	X	X
501	X	X	X	X	X
502	X	X	X	X	X
503	X	X	X	X	X
504	X	X	X	X	X
505	X	X	X	X	X
506	X	X	X	X	X
507	X	X	X	X	X
508	X	X	X	X	X
509	X	X	X	X	X
510	X	X	X	X	X
511	X	X	X	X	X
512	X	X	X	X	X
513	X	X	X	X	X
514	X	X	X	X	X
515	X	X	X	X	X
516	X	X	X	X	X
517	X	X	X	X	X
518	X	X	X	X	X

Table 3c - Continued

R2 \ R1	44	46	47	51	50
519	X	X	X	X	X
520	X	X	X	X	X
521	X	X	X	X	X
522	X	X	X	X	X
523	X	X	X	X	X
524	X	X	X	X	X
525	X	X	X	X	X
526	X	X	X	X	X
527	X	X	X	X	X
528	X	X	X	X	X
529	X	X	X	X	X
530	X	X	X		X
531	X	X	X		X
532	X	X	X		
533	X	X	X		X
534	X	X	X	X	X
535	X	X		X	X
536	X	X		X	X

Table 3d

Table 3d is directed to compounds of the formula (ID):



(ID)

wherein R^1 and R^2 are as defined in Table 3d.

An "X" in the box formed by the intersection of the R^2 and the R^1 row represents an R^2 and R^1 combination of a compound of formula ID that is included in the definition of the compounds of formula I useful in the methods of this invention. For example, compounds of formula ID wherein R^2 is moiety 3 (see Table 2 for definition) and R^1 is moiety 46 (see Table 1 for definition) are included in the definition of formula I (there is an "X" in the box formed by the intersection of the R^2 column and the R^1 row).

If there is no "X" in the box, then that compound is excluded from the definition of the compounds of formula I. For example, compounds of formula ID wherein

moiety R^2 is 83 and moiety R^1 is 46 (no "X" in the box formed by the intersection of the R^2 column and the R^1 row) are excluded from the definition of the compounds of formula I.

Table 3d

R2 \ R1	46	48
3	X	X
5	X	X
16	X	X
20	X	X
22	X	X
30	X	X
35	X	X
44	X	X
47	X	X
48	X	X
55	X	X
59	X	X
60	X	X
64	X	X
68	X	X
83		X
84	X	X
85		X
133		X
134	X	X
135	X	X
136	X	X
138	X	X
139	X	X
140	X	X
141	X	X
144	X	X
146	X	X
152	X	X
157	X	X
167	X	X
175	X	X
189	X	X
198	X	X
200	X	X
202	X	X
217	X	X
218	X	X
219	X	X
223	X	X

R2 \ R1	46	48
224	X	X
225	X	X
226	X	X
227	X	X
230	X	X
236	X	X
242	X	X
245		X
248	X	X
251	X	X
258	X	X
260	X	X
263	X	X
329	X	X
384	X	X
385	X	X
386	X	X
387	X	X
388	X	X
389	X	X
390	X	X
391	X	X
392	X	X
393	X	X
394	X	X
395	X	X
396	X	X
397	X	X
398	X	X
399	X	X
400	X	X
401	X	X
402	X	X
403	X	X
404	X	X
405	X	X
406	X	X
407	X	X
408	X	X

Table 3d - Continued

R2 \ R1	46	48
409	X	X
410	X	X
411	X	X
412	X	X
413	X	X
414	X	X
415	X	X
416	X	X
417	X	X
418	X	X
419	X	X
420	X	X
421		X
422	X	X
423	X	X
424	X	X
425	X	X
426	X	X
427	X	X
428	X	X
429	X	X
430	X	X
431	X	X
432	X	X
433		X
434	X	X
435		X
436		X
437	X	X
438		X
469	X	X
470	X	X
471	X	X
472	X	X
473	X	
474	X	X
475	X	
476	X	X
477	X	X

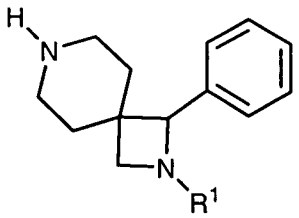
R2 \ R1	46	48
478	X	X
479	X	X
480	X	X
481	X	X
482	X	X
483	X	X
484	X	X
485	X	X
486	X	X
487		X
489	X	X
490	X	X
491	X	X
492	X	X
493	X	X
494		X
495	X	X
496	X	X
497		X
498	X	
500	X	X
501	X	X
502	X	X
503	X	X
504	X	X
505	X	X
506	X	X
507	X	X
508	X	X
509	X	X
510	X	X
511	X	X
512	X	X
513	X	X
514	X	X
515	X	X
516	X	X
517	X	X
518	X	X

Table 3d - Continued

R2 \ R1	46	48
519	X	X
520	X	X
521	X	X
522	X	X
523	X	X
524	X	X
525	X	X
526	X	X
527	X	X
528	X	X
529	X	X
530	X	X
531	X	X
532	X	X
533	X	X
534	X	X
535	X	
536	X	

Table 4a

Table 4a is directed to compounds of the formula (IE):



(IE)

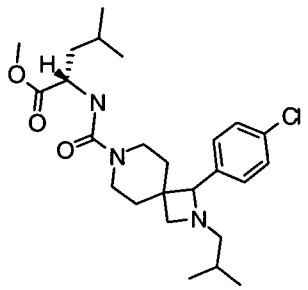
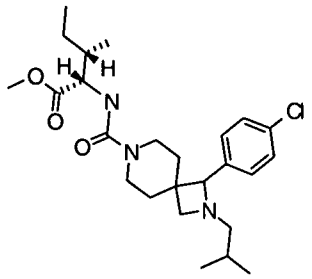
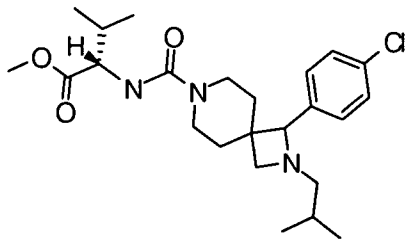
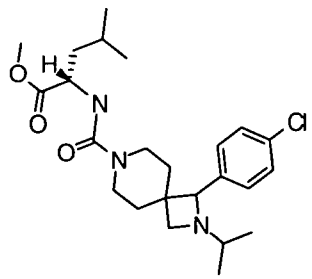
wherein R^1 is as defined in Table 4a.

The compounds defined by Table 4a are included in the definition of the compounds of formula I useful in the methods of this invention.

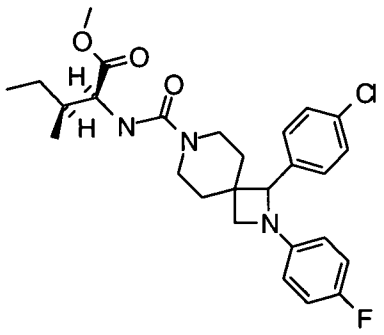
Table 4a	
R1	R1
19	67
21	68
22	69
25	70
29	71
31	72
34	73
35	74
43	75
53	76
54	77
55	78
56	79
57	80
58	81
59	82
60	83
61	84
62	85
63	86
64	87
65	88
66	89
67	90
	91
	93

Representative compounds of the invention include, for example, the compounds in Table 5. In the Cav3.2 Ionworks assay the IC_{50} of the compounds in Table 5 were within the range of 23 to 23506 nM

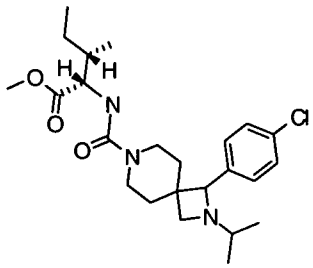
Table 5

Compounds of Formula I
(1) 
(2) 
(3) 
(4) 

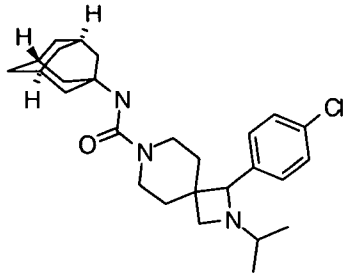
(5)



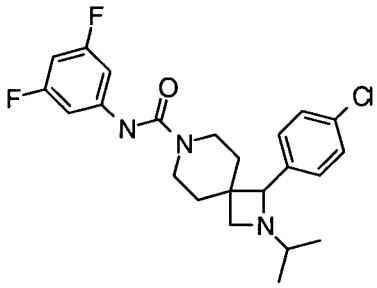
(6)



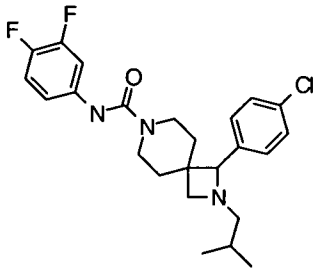
(7)



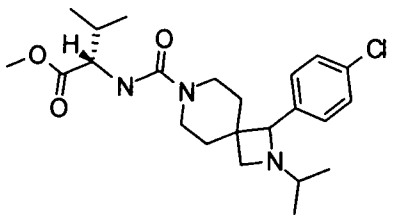
(8)



(9)



(10)



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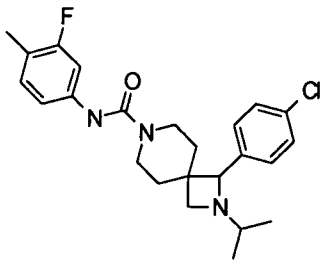

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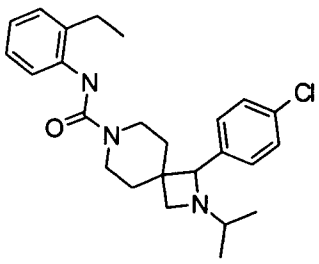

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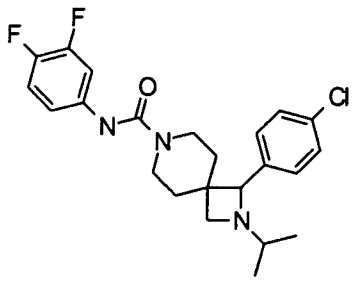

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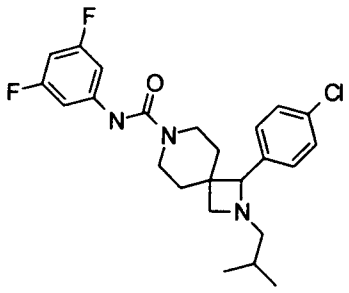
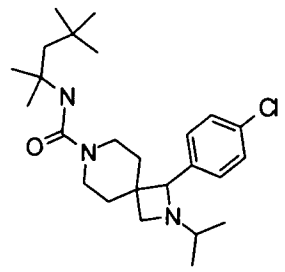
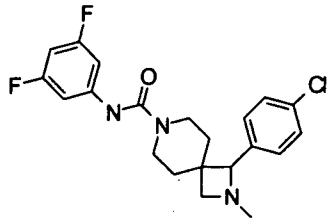
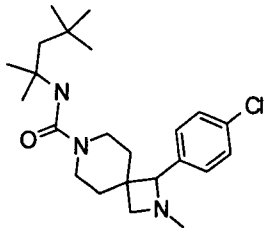
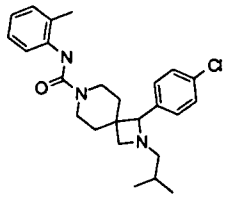
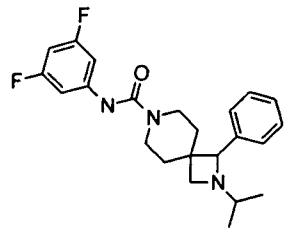
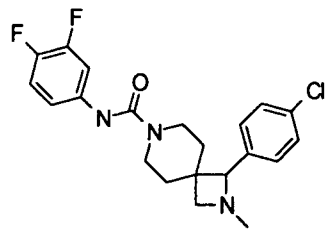
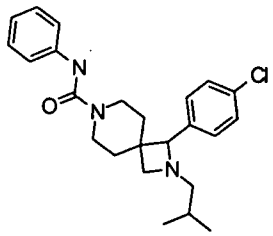
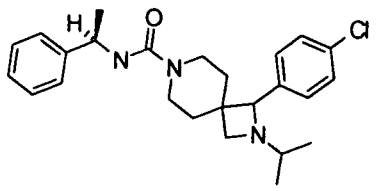
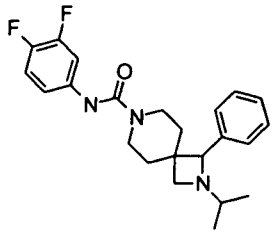
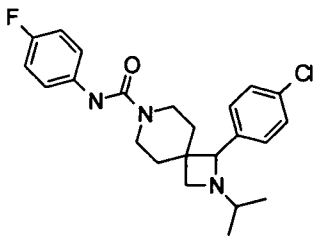
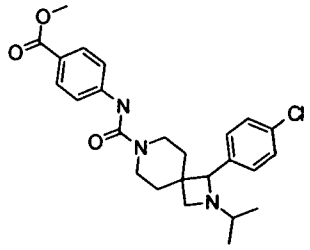
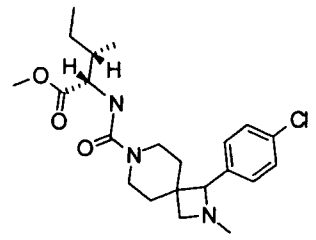
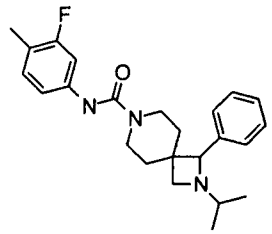
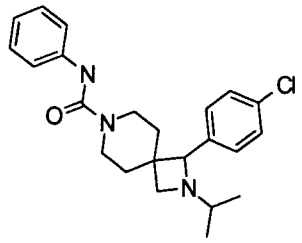
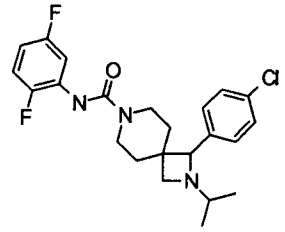
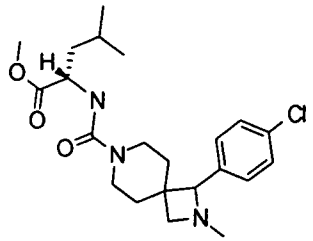
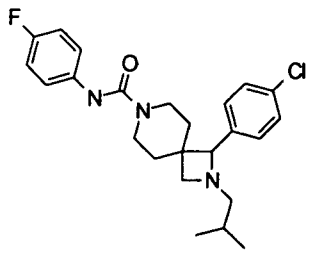
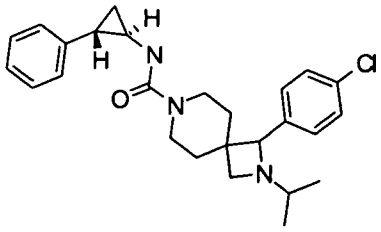


(15)	
(17)	
(18)	
(19)	

(20)	
(22)	
(24)	

(25)	
(27)	
(28)	
(29)	

(30)	
(32)	
(33)	
(34)	

(35)	
(36)	
(39)	

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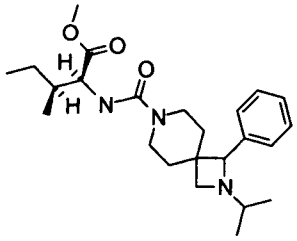

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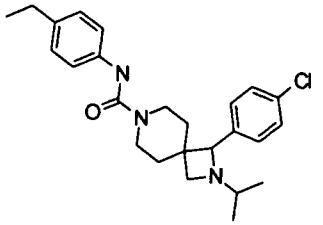

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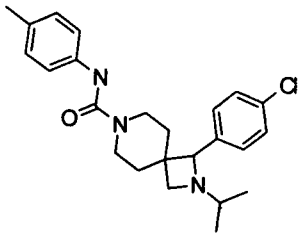

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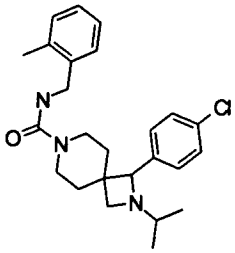

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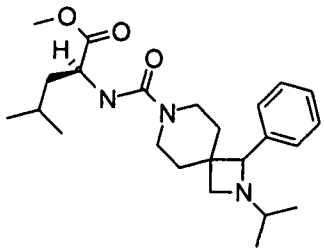
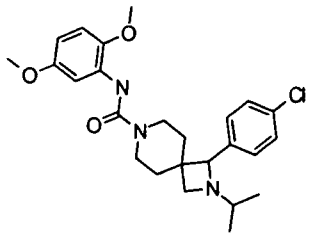
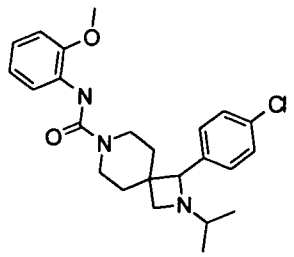
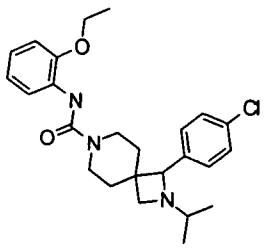
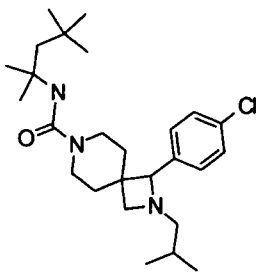
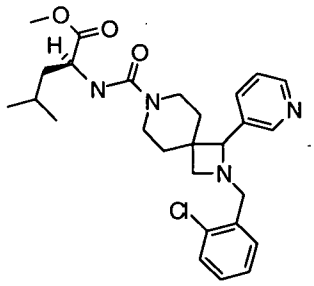
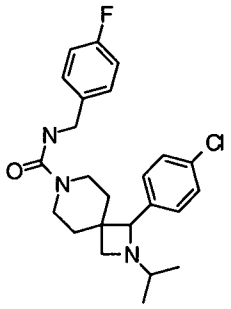
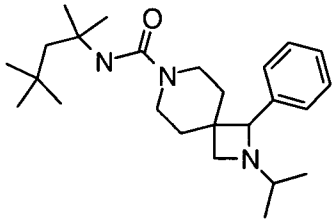
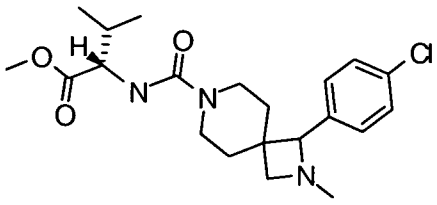
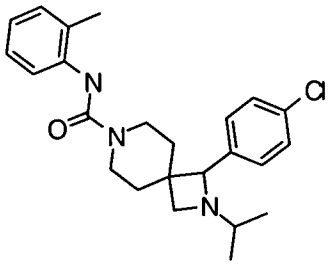


(46)	
(47)	
(48)	
(49)	

(50)	
(51)	
(52)	
(53)	
(54)	

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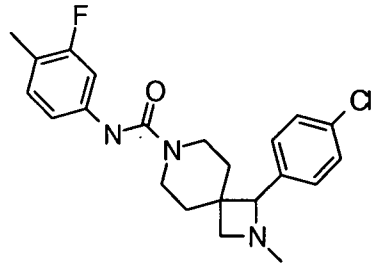

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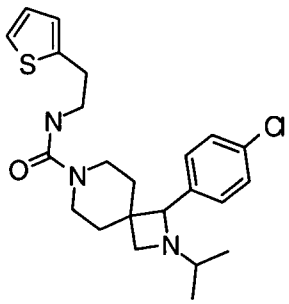

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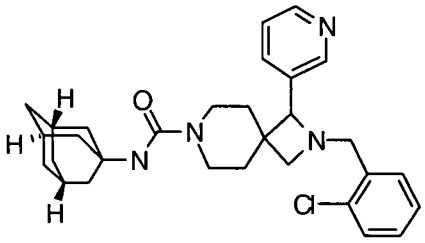

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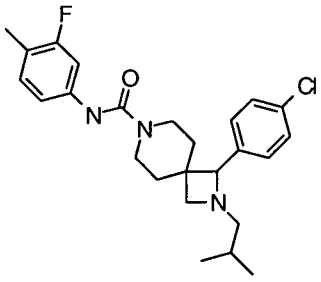

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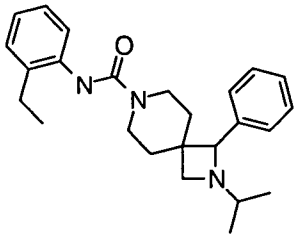
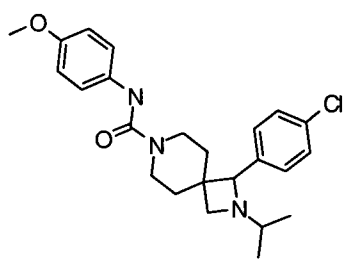
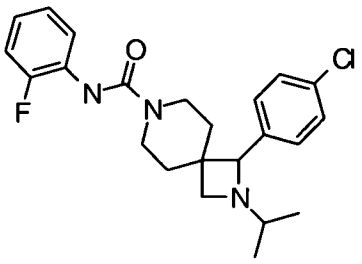
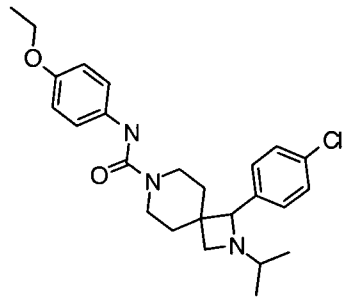
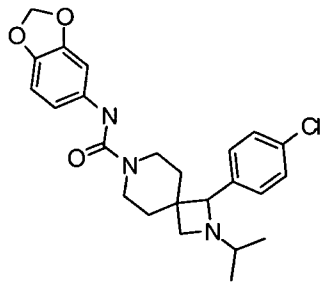
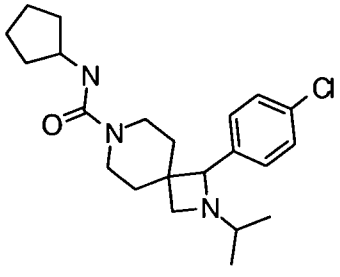


(60)	
(61)	
(62)	
(63)	
(64)	

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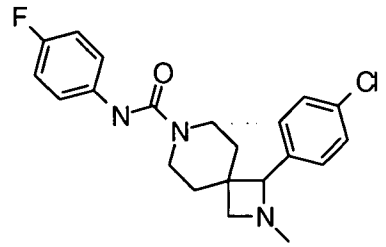

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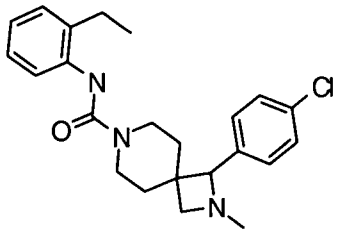

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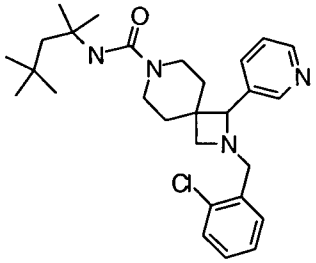

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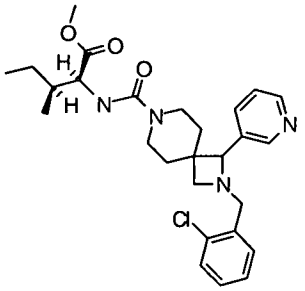

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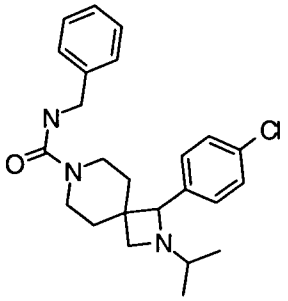
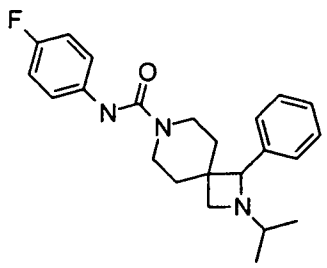
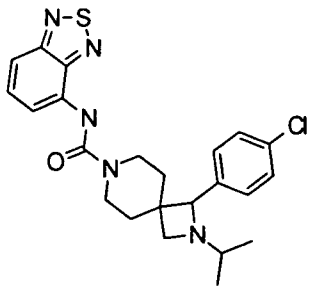
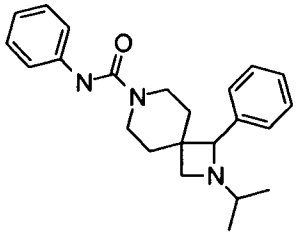
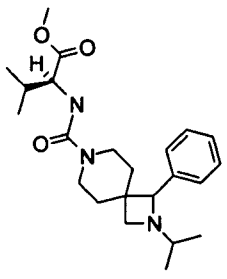
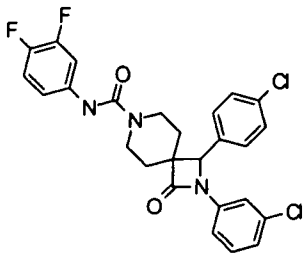
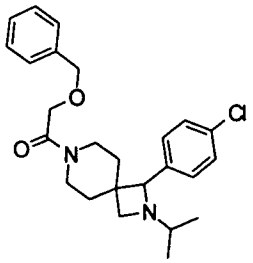
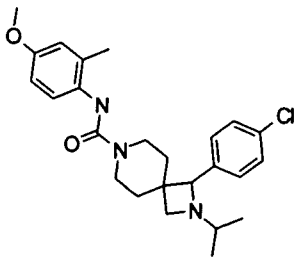
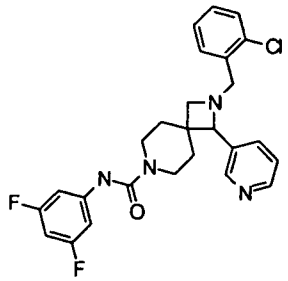
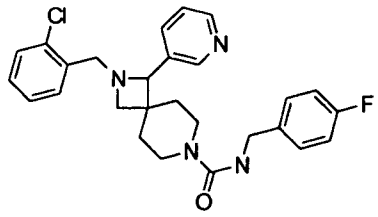
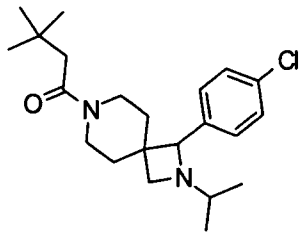
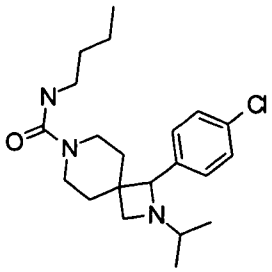
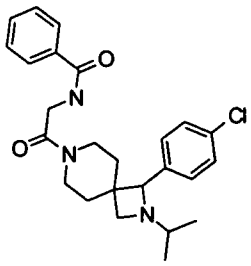
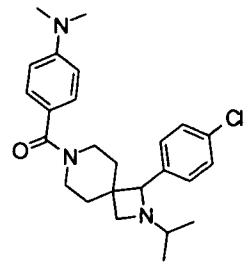
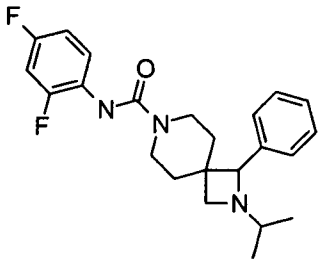
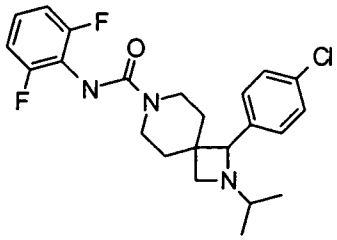
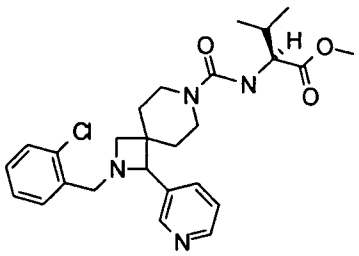
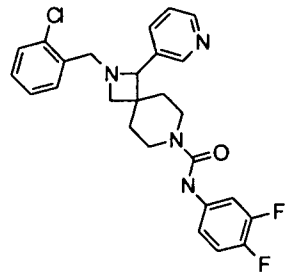
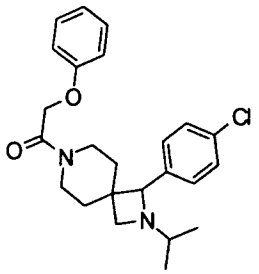
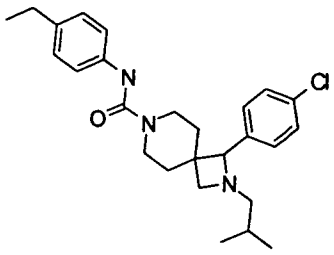
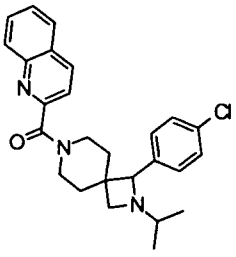


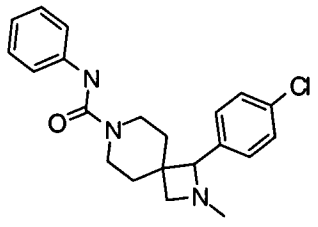
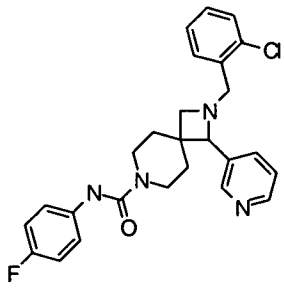
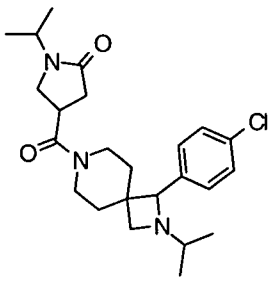
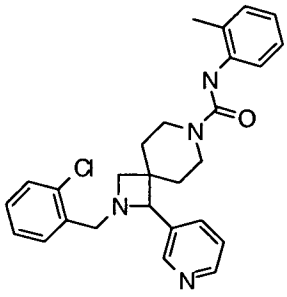
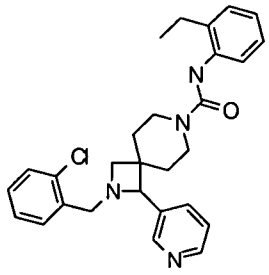
(70)	
(71)	
(72)	
(74)	

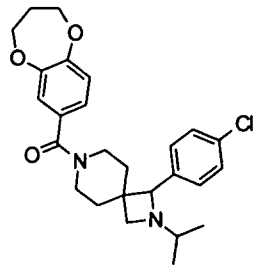
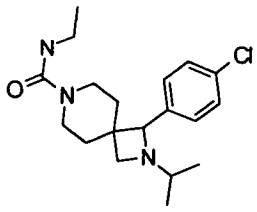
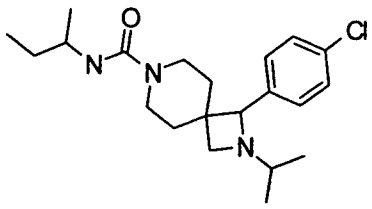
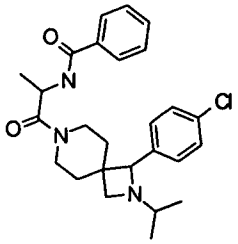
(75)	
(76)	
(77)	
(79)	

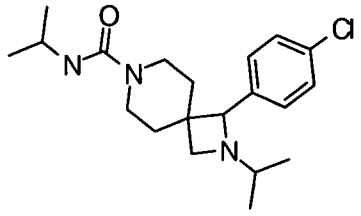
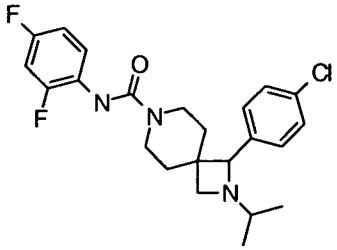
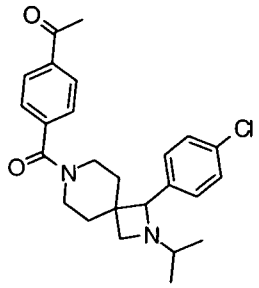
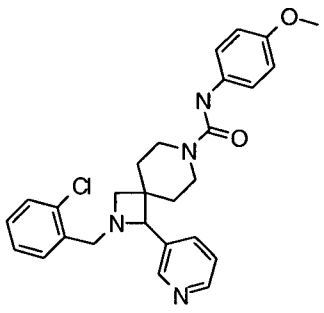
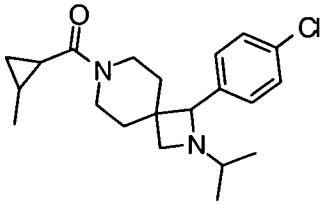
(81)	
(82)	
(83)	
(84)	

(86)	
(87)	
(88)	
(89)	

(90)	
(92)	
(93)	
(94)	

(95)	
(96)	
(97)	
(98)	
(99)	

(100)	
(102)	
(103)	
(104)	

(105)	
(106)	
(107)	
(108)	
(109)	

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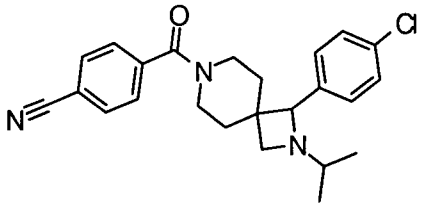

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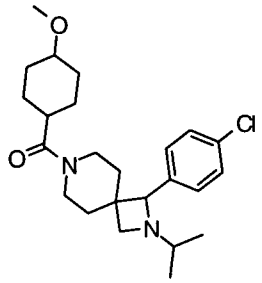

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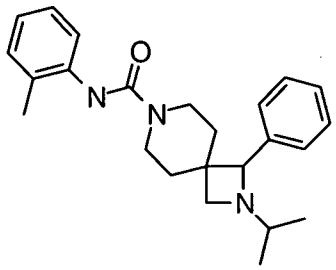

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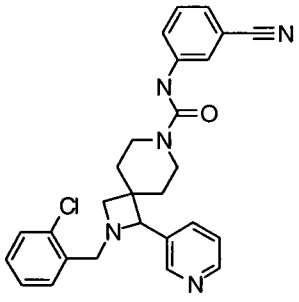
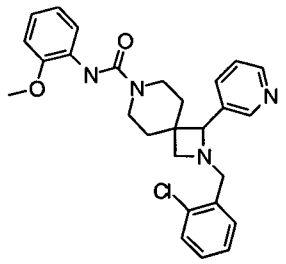
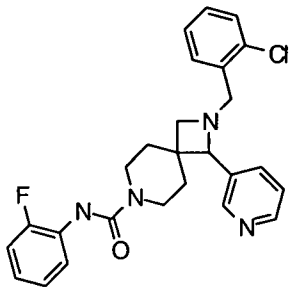
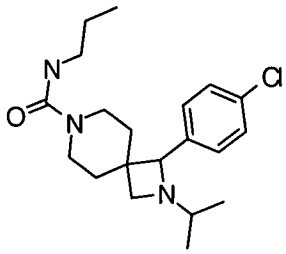
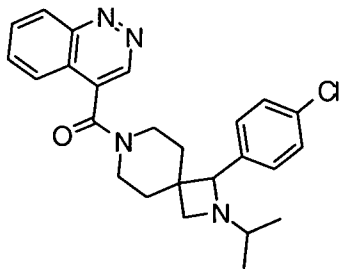
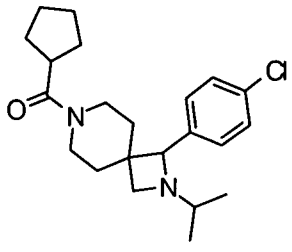


(114) 
(115) 
(116) 
(117) 
(118) 

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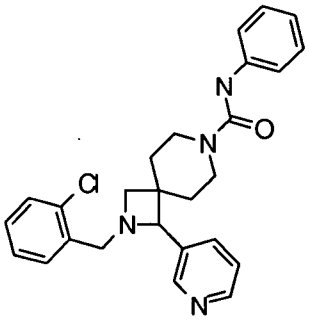

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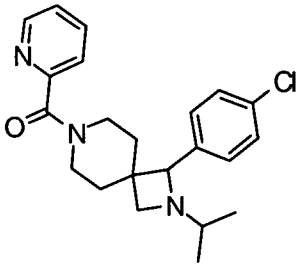

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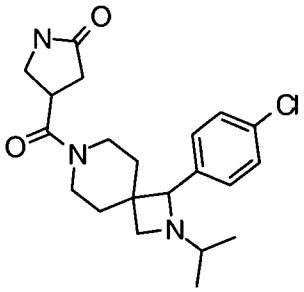

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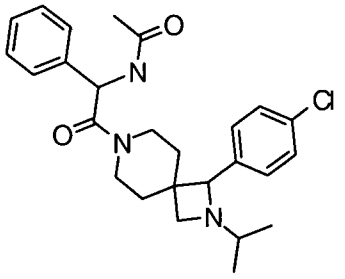
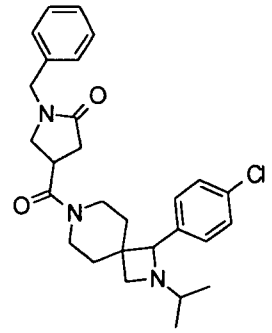
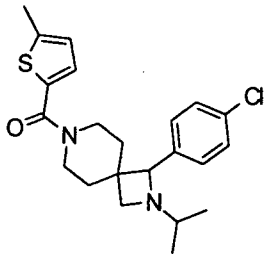
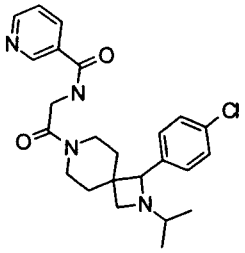
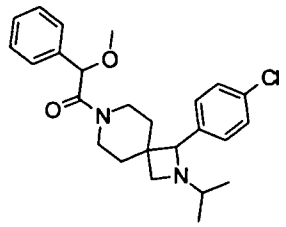
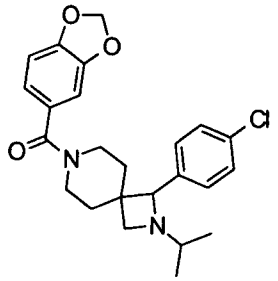
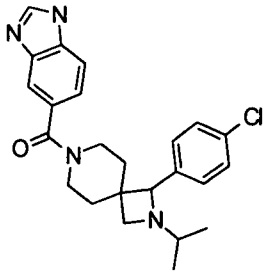
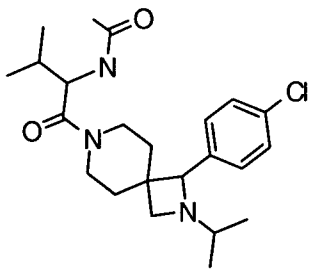
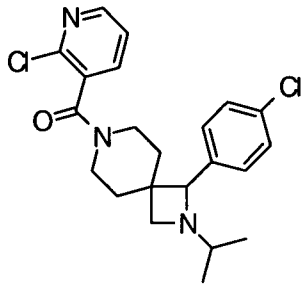
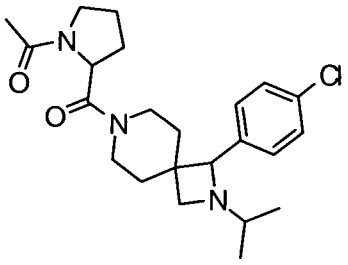
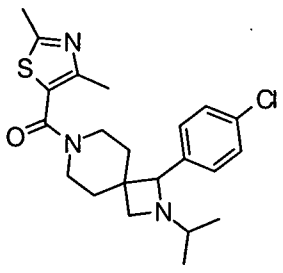
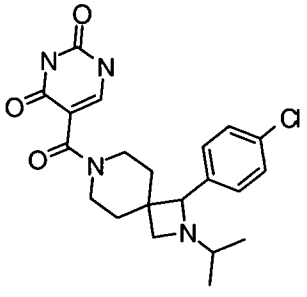


(123)	
(124)	
(125)	

(127)	
(128)	
(129)	

(131)	
(132)	
(133)	
(134)	
(135)	

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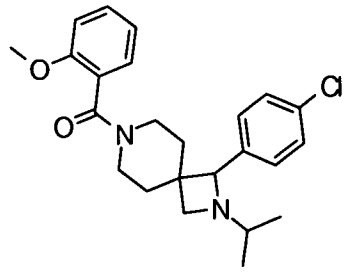

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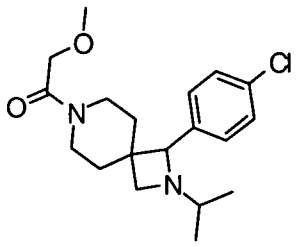

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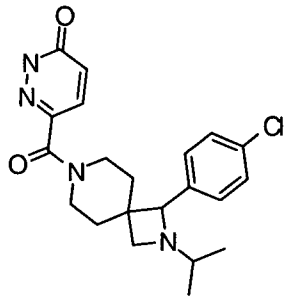

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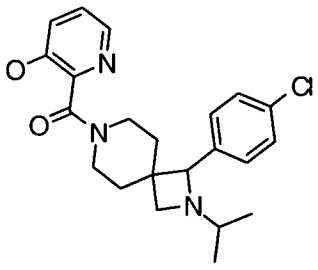

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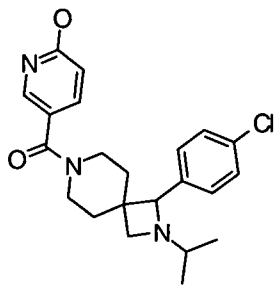
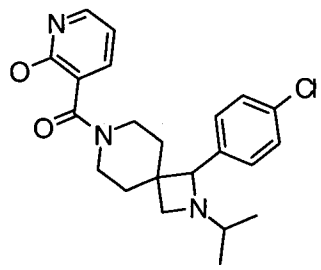
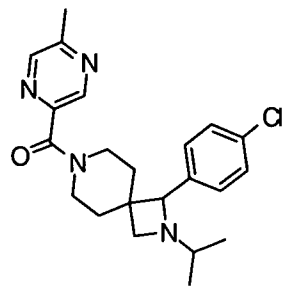
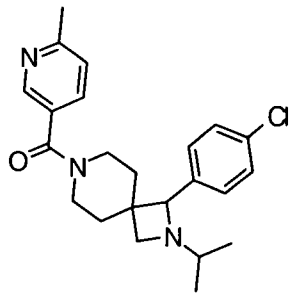
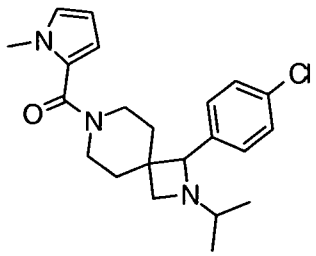
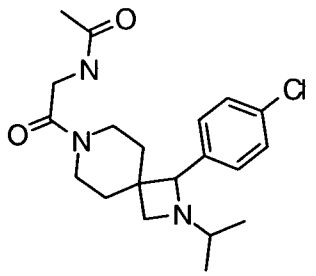
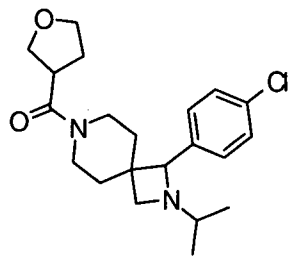
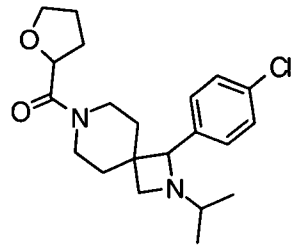
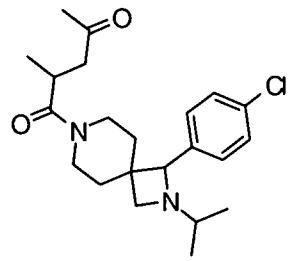
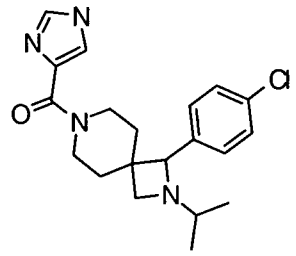
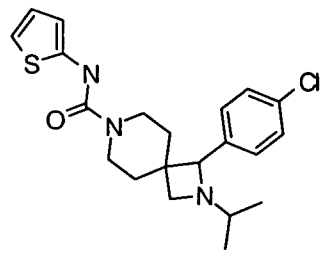
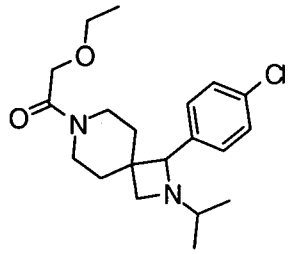
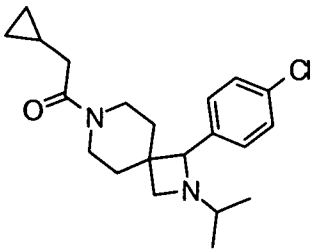
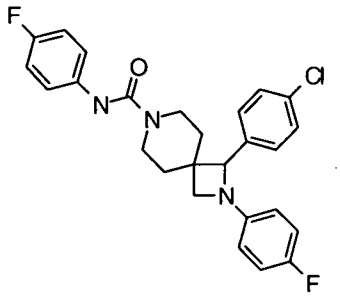
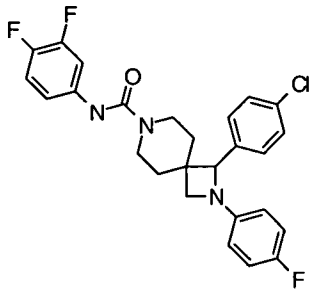
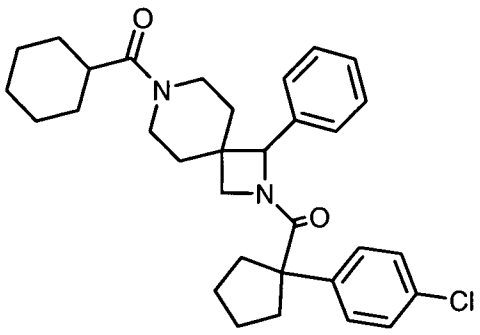


(141)	
(142)	
(143)	
(144)	
(145)	

(146)	
(147)	
(148)	
(149)	
(150)	

(151) 
(152) 
(153) 
(154) 
(154.1) 

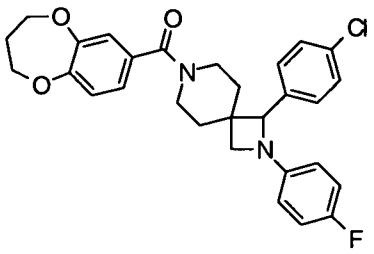
Representative compounds useful in the methods of this invention are also given in Table 6. The GPR 119 cAMP IC_{50} activity for compounds in Table 6 were within the range of: 1640 to 16,260 nM.

5

TABLE 6

Compound of Formula I

(155)



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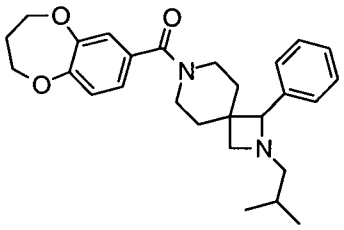

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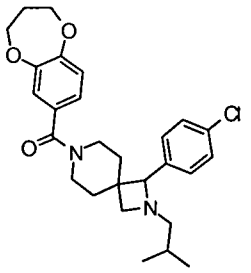

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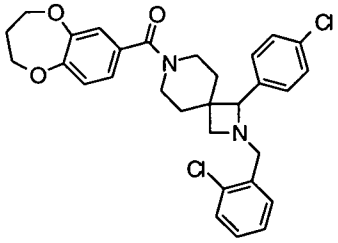
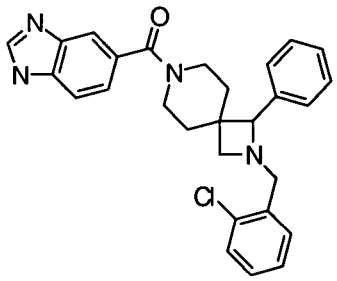
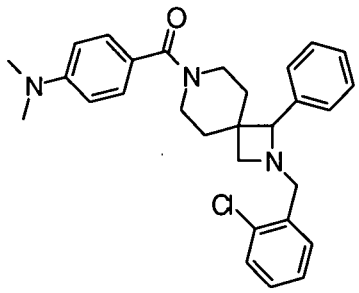
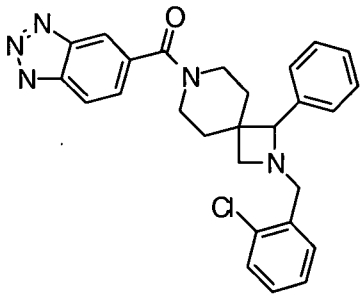
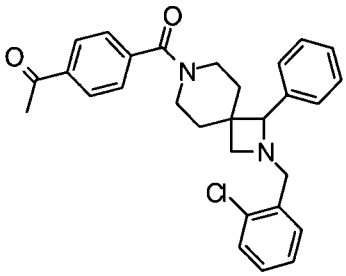
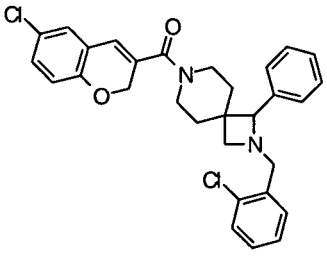


(159) 

(160) 

(161) 

(162) 

(163) 

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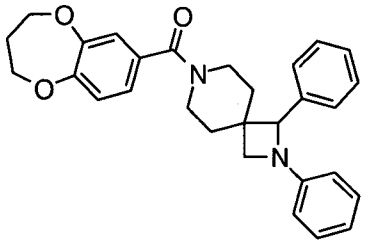

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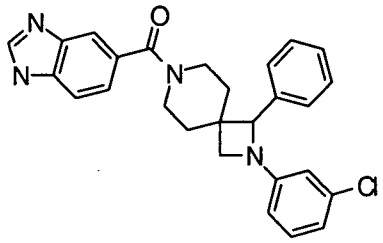

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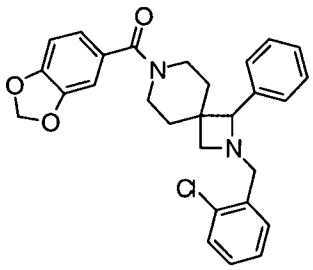

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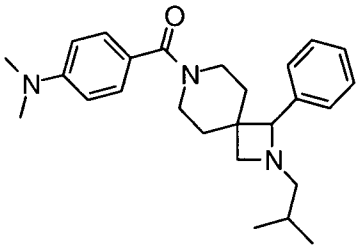

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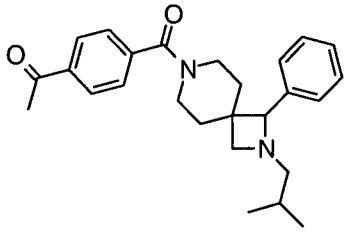

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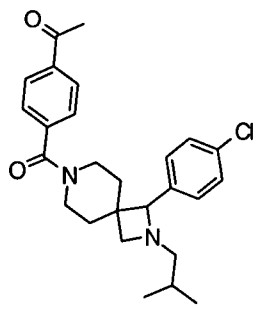

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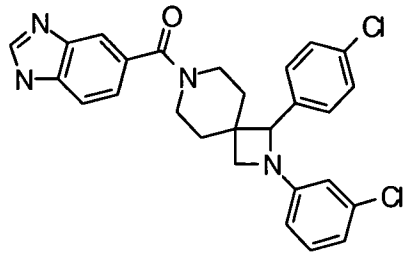

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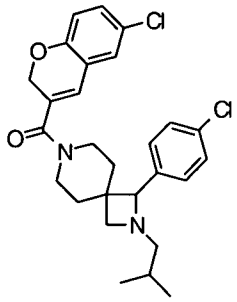

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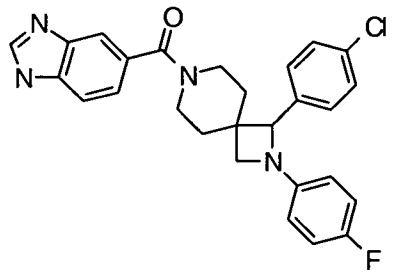

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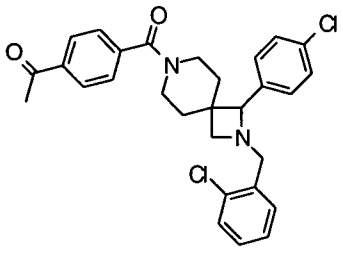

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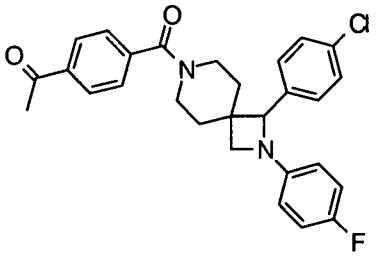

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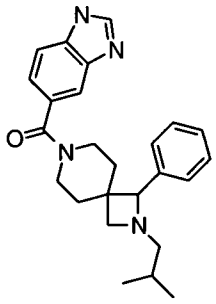

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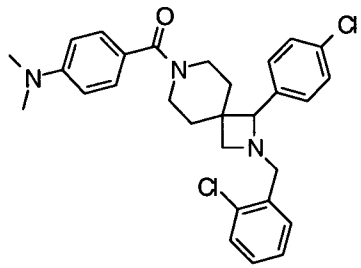

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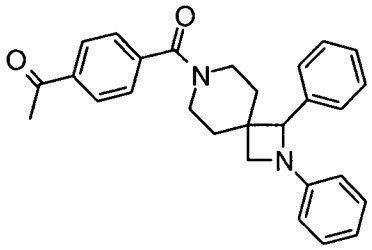

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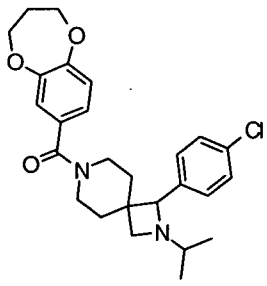

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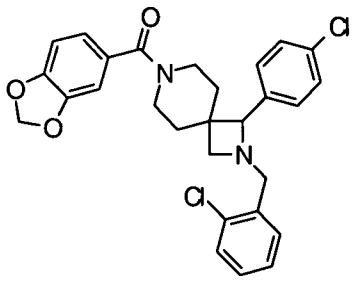

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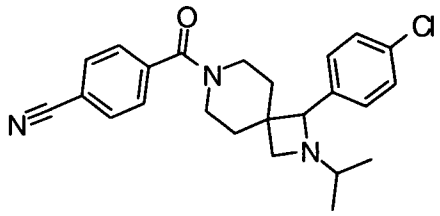

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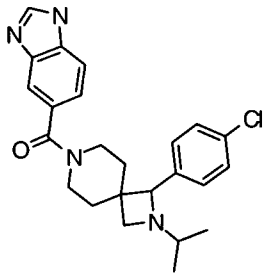

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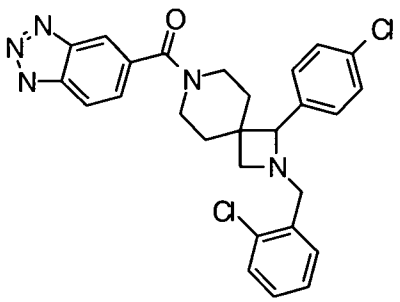

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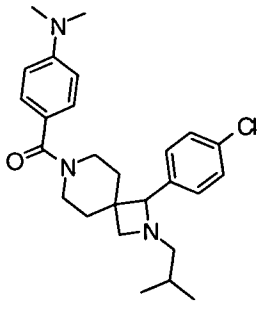

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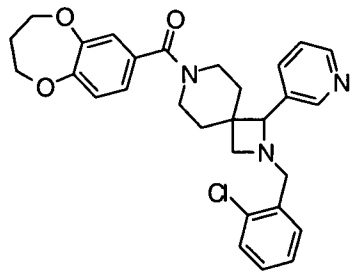

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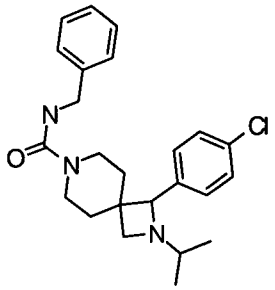

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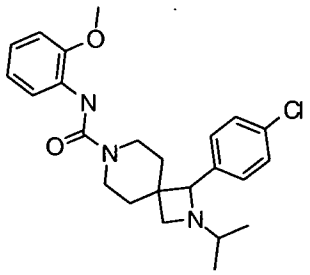

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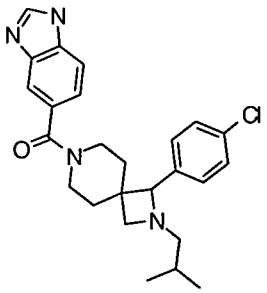

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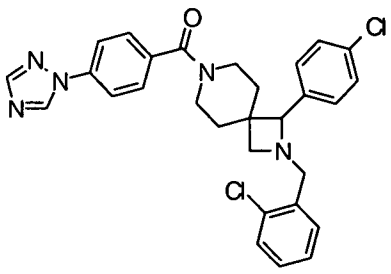

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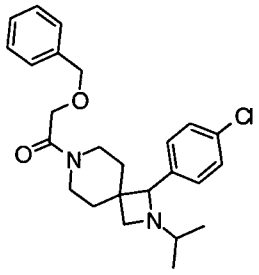

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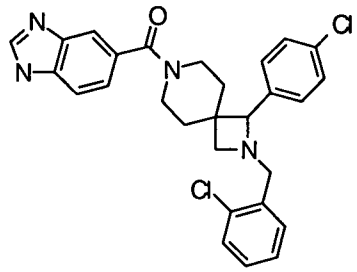

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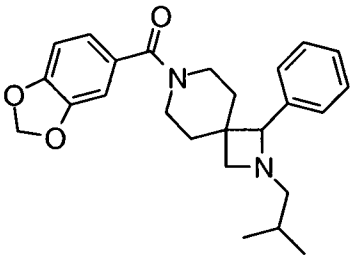

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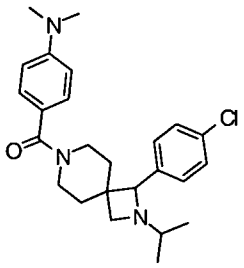

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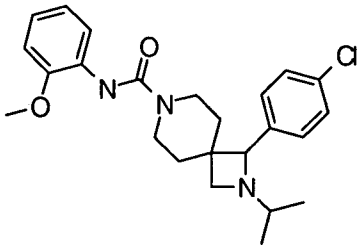

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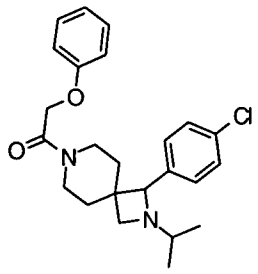

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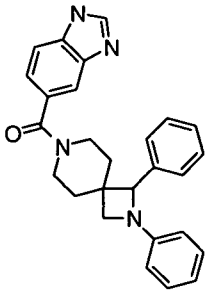

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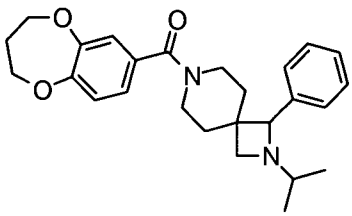

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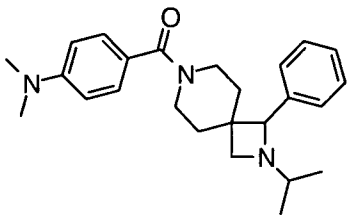

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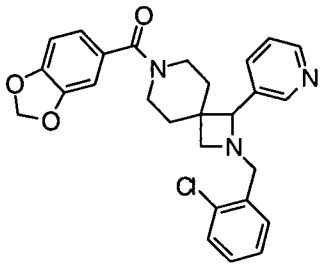

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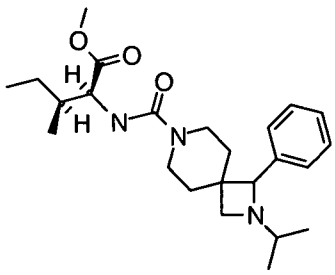

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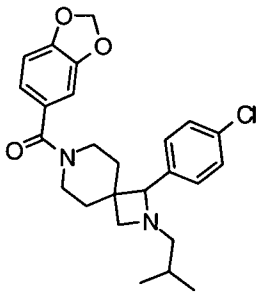

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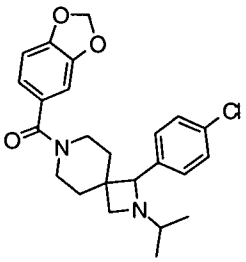

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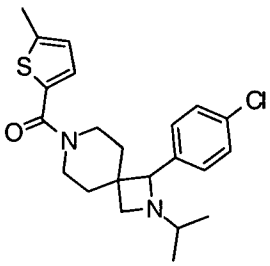

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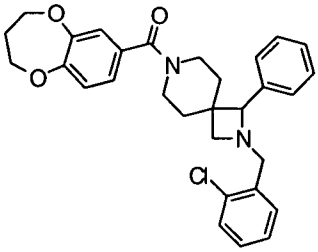
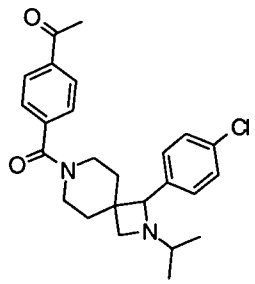


(204) 

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"At least one" compound of formula I means 1, 2, 3 or 4 different compounds, but preferably one compound of formula I is used in the claimed methods. Similarly, when "at least one" is used in connection with the additional agents used in the combinations, 1, 2, 3 or 4 additional agents are contemplated, but preferably one or two, more preferably one additional agent is used.

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

"PG" means protecting group.

"Mammal" means humans and other mammalian animals.

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

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

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

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

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

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

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

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

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

One or more compounds of formula I may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of formula I may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al, J.*

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

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

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

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are

generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

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

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

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

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

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

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

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

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates

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

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

Certain isotopically-labelled compounds of Formula I or II (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula I can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

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

Those skilled in the art will appreciate that for some of the compounds of Formula I, one isomer will show greater pharmacological activity than other isomers.

One to three compounds of formula I can be administered in the methods of the invention, preferably one.

For preparing pharmaceutical compositions from the compounds described for use in the methods of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible

granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

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

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

The compounds for use in the present invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound of formula I is administered orally.

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

The quantity of active compound of formula I in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally,

treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of formula I will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen for compounds of formula I is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to provide relief from the diseases or conditions listed above.

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

Additional agents udeful for treating pain include non-opioid (also known as non-steroidal anti-inflmmatories) analgesics such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusinal, and naproxen; opioid analgesics such as morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone; steroids such as prednisolone, fluticasone, triamcinolone, beclomethasone, mometasone, budisamide, betamethasone, dexamethasone, prednisone, flunisolide and cortisone; COX-I inhibitors such as aspirin and piroxicam; COX-II inhibitors such as rofecoxib, celecoxib, valdecoxib and etoricoxib; agents useful for treating inflammatory bowel disease such as IL-10, steroids, and azulfidine; and agents useful for treating rheumatoid arthritis such as methotrexate, azathioprine, cyclophosphamide, steroids and mycophenolate mofetil.

Especially preferred agents for treating neuropathic pain are opioid and non-opioid analgesics, including acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusinal, naproxen, morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone. Especially preferred agents for treating inflammatory pain are steroids and non-opioid analgesic agents.

Examples of the drugs for use in combination with compounds of formula I for treating Type II diabetes include sulfonylureas, insulin sensitizers (such as PPAR agonists, DPPIV inhibitors, PTP-1B inhibitors and glucokinase activators), α-glucosidase inhibitors, insulin secretagogues, hepatic glucose output lowering compounds, and insulin.

The activators or agonists of PPAR are described above.

Non-limiting examples of sulfonylurea drugs include glipizide, tolbutamide, glyburide, glimepiride, chlorpropamide, acetohexamide, gliamilide, gliclazide, glibenclamide and tolazamide. Insulin sensitizers include PPAR-γ agonists described in detail above, preferably troglitazone, rosiglitazone, pioglitazone and englitazone; biguanidines such as metformin and phenformin; DPPIV inhibitors such as sitagliptin, saxagliptin, denagliptin and vildagliptin; PTP-1B inhibitors; and glucokinase activators. α-Glucosidase inhibitors that can be useful in treating type II diabetes include miglitol, acarbose, and voglibose. Hepatic glucose output lowering drugs include Glucophage and Glucophage XR. Insulin secretagogues include sulfonylurea and non-sulfonylurea drugs such as GLP-1, exendin, GIP, secretin, glipizide, chlorpropamide, nateglinide, meglitinide, glibenclamide, repaglinide and glimepiride. Insulin includes all formualtions of insulin, including long acting and short acting forms of insulin.

Compounds of the invention may be administered in combination with anti-obesity agents for the treatment of diabetes. Examples of anti-obesity agents include CB1 antagonists or inverse agonists such as rimonabant, neuropeptide Y antagonists, MCR4 agonists, MCH receptor antagonists, histamnine H3 receptor antagonists or inverse agonists, leptin, appetite suppressants such as sibutramine, and lipase inhibitors such as xenical.

For treating diabetes, compounds of the invention may also be administered in combination with antihypertensive agents, for example β-blockers and calcium channel blockers (for example diltiazem, verapamil, nifedipine, amlopidine, and mybefradil), ACE inhibitors (for example captopril, lisinopril, enalapril, spirapril,

ceranopril, zefenopril, fosinopril, cilazopril, and quinapril), AT-1 receptor antagonists (for example losartan, irbesartan, and valsartan), renin inhibitors and endothelin receptor antagonists (for example sitaxsentan).

Certain meglitinide drugs lower blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning β cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations. The meglitinide drugs close ATP-dependent potassium channels in the β cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the β cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. Non-limiting examples of suitable meglitinide drugs include repaglinide and nateglinide.

Non-limiting examples of suitable antidiabetic medications that sensitize the body to the insulin that is already present include certain biguanides and certain glitazones or thiazolidinediones. Certain suitable biguanides lower blood sugar by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity (increasing peripheral glucose uptake and utilization). A non-limiting example of a suitable biguanide is metformin. Non-limiting examples of metformin include metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride, such as GLUCOPHAGE® Tablets from Bristol-Myers Squibb); metformin hydrochloride with glyburide, such as GLUCOVANCE™ Tablets from Bristol-Myers Squibb); buformin.

Non-limiting examples of antidiabetic medications that slow or block the breakdown of starches and certain sugars and are suitable for use in the compositions of the present invention include alpha-glucosidase inhibitors and certain peptides for increasing insulin production. Alpha-glucosidase inhibitors help the body to lower blood sugar by delaying the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. Non-limiting examples of suitable alpha-glucosidase inhibitors include acarbose; miglitol; camiglibose; certain polyamines as disclosed in WO 01/47528 (incorporated herein by reference); voglibose. Non-limiting examples of suitable peptides for increasing insulin production including amlintide (CAS Reg. No. 122384-88-7 from Amylin; pramlintide, exendin, certain compounds having Glucagon-like peptide-1 (GLP-1) agonistic activity as disclosed in WO 00/07617 (incorporated herein by reference).

Non-limiting examples of additional antidiabetic medications include orally administrable insulin. Non-limiting examples of suitable orally administrable insulin or insulin containing compositions include AL-401 from AutoImmune, and certain compositions as disclosed in U.S. Patent Nos. 4,579,730; 4,849,405; 4,963,526; 5,642,868; 5,763,396; 5,824,638; 5,843,866; 6,153,632; 6,191,105; and WO 85/05029 (each of which is incorporated herein by reference).

The antidiabetic medications are administered in a therapeutically effective amount to treat the specified condition, for example in a daily dose preferably ranging from about 1 to about 3000 mg per day, and more preferably about 50 to about 2000 mg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

In the Schemes and examples that follow, the following abbreviations are used: Ac (acetyl); Me (methyl); Et (ethyl); Ph (phenyl); Bn (benzyl); Boc (tert-butoxycarbonyl); DCE (dichloroethane); DMSO (d_6-dimethylsulfoxide); DIPEA (diisopropylethylamine); Dioxane (1,4-dioxane); EtOAc (ethyl acetate); EtOH (ethanol); Ether (diethyl ether); HOBT (1-hydroxybenzotriazole hydrate); IPA (isopropyl alcohol); LCMS (liquid chromatography mass spectrometry); LDA (lithium diisopropylamide); LHMSD (lithium bis(trimethylsilyl)amide); MeOH (methanol); RT (Room temperature, about 25°C); SiO_2 (silica gel for flash chromatography); TFA (trifluoroacetic acid); TLC (thin layer chromatography); THF (tetrahydrofuran).

The compounds useful in the methods of the invention can be made according to the processes described below. The compounds useful in the methods of this invention can also be made by the examples below, which examples should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

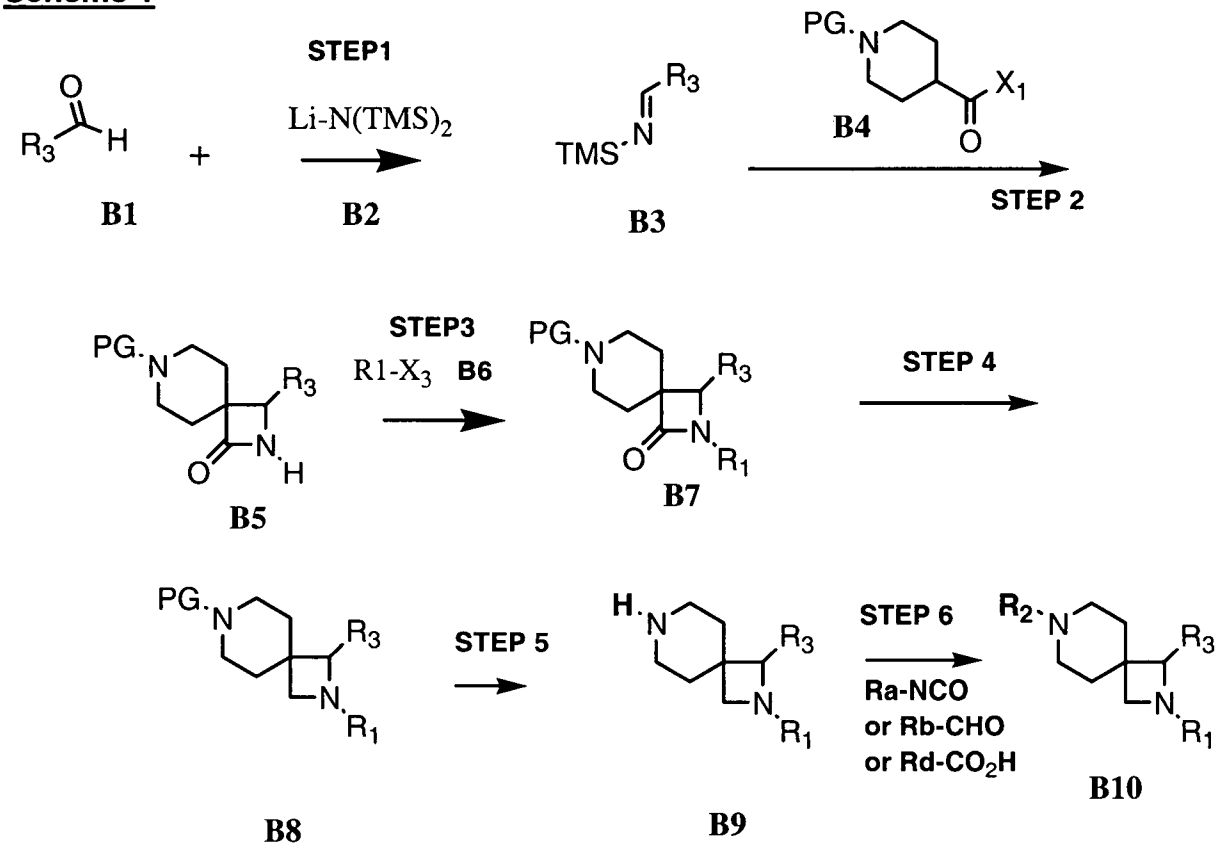
General Methods

The general methods described in this paragraph were used unless stated otherwise in the examples below. All solvents and reagents were used as received. Proton NMR spectra were obtained using a Varian XL-400 (400 MHz) instrument and

were reported as parts per million (ppm) downfield from Me_4Si. LCMS analysis was performed using an Applied Biosystems API-100 mass spectrometer equipped with a Shimadzu SCL-10A LC column: Altech platinum C18, 3 um,33 mm X 7 mm ID; gradient flow: 0 min, 10% CH_3CN; 5 min, 95% CH_3CN; 7 min, 95% CH_3CN; 7.5 min, 10% CH_3CN; 9 min, stop. Flash column chromatography was performed using Selecto Scientiic flash silica gel, 32–63 mesh. Analytical and preparative TLC was performed using Analtech Silica gel GF plates. Chiral HPLC was performed using a Varian PrepStar system equipped with a Chiralpak OD column (Chiral Technologies).

GENERAL SYNTHETIC ROUTES

Scheme 1

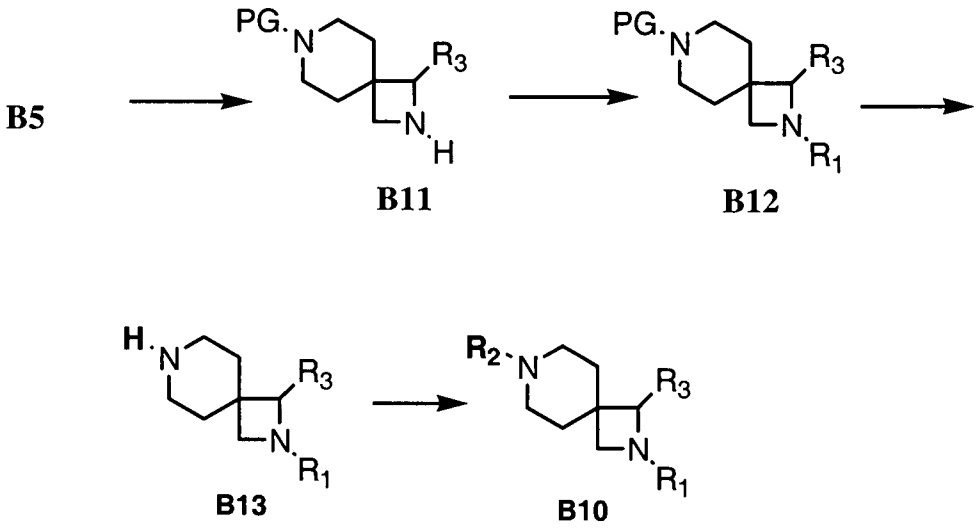


Compound of formula **B1** can be treated with a compound of formula **B2** to provide compound of formula **B3**. Compound of formula **B4** can be treated with a base such as LDA or LHMDS at -78 °C followed by treatment with a compound of formula **B3** at room temperature to provide compound of formula **B5**. Compound of formula **B6** (where X3 is a leaving group such as halogen or triflate, for example) can be converted into a compound of formula **B7** by the treatment with a compound of formula **B5** and a base such as NaH. Compound **B7** is then reduced with reagents such as $LiAlH_4$, $LiAH_4/AlCl_3$, diborane or a mixture of diphenylsilane and

hydridocarbonyltris(triphenylphosphine) rhodium(I) to provide compound **B8,** which is elaborated into **B9** by treatment with TFA. Compounds of type **B9** are treated with a carboxylic acid, or an aldehyde or an isocyanate in the presence of an apprpropriate coupling agent such as a carbodimide, or reducing agent such as sodium triacetoxyborohydride as needed to prepare compounds of formula **B10**.

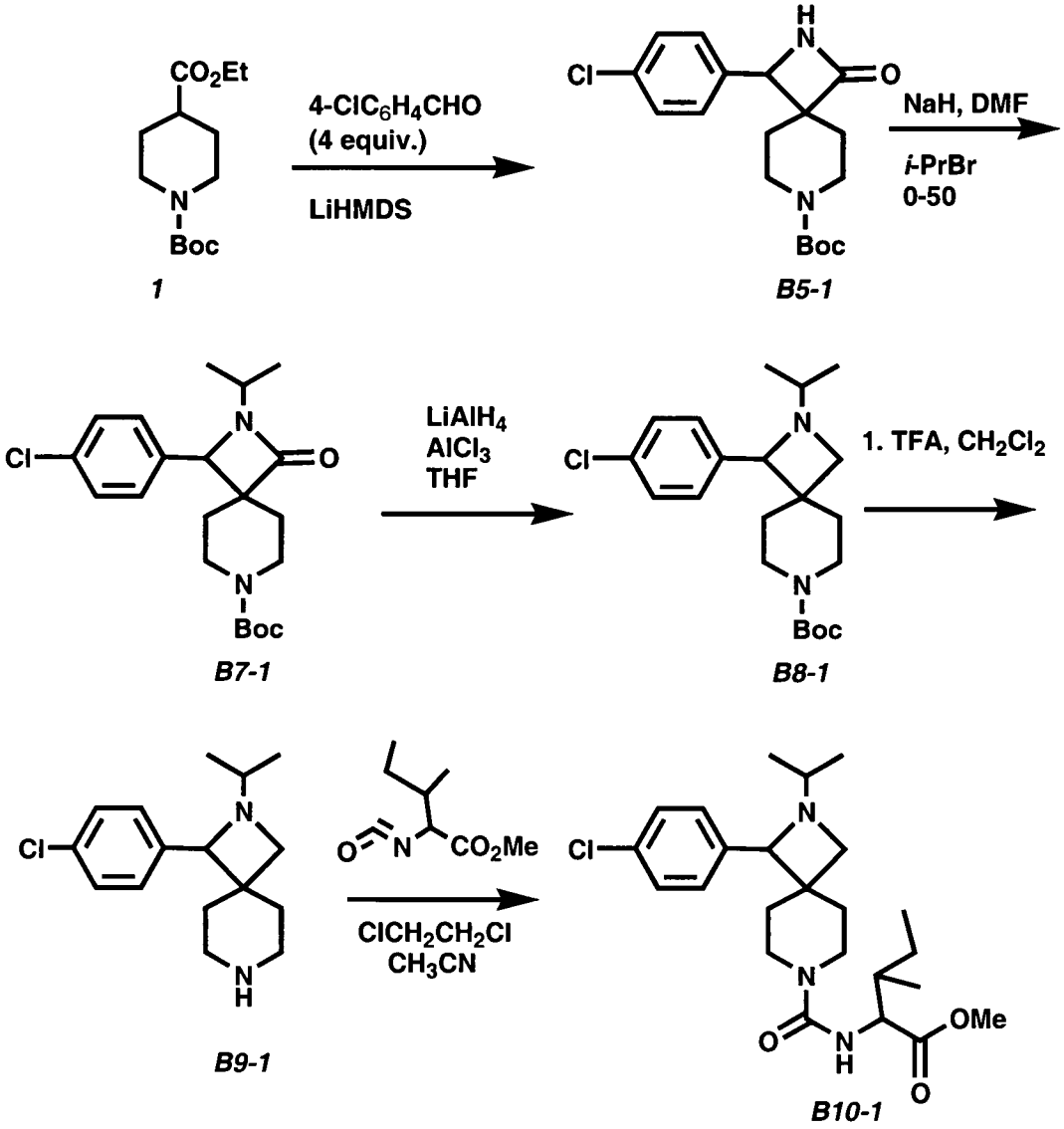
Additionally, compounds of type B5 can be converted into compounds B11 by treatment with reducing agents such as LiAH4 and AlCl3 and then converted into compounds **B12** by reaction with a carboxylic acid, or an aldehyde or an isocyanate in the presence of an apprpropriate coupling agent such as a carbodimide, or reducing agent such as sodium triacetoxyborohydride as needed. to prepare compounds of formula **B12.** Removal of the protecting group from **B12** by treatment with an acid such as TFA and reaction of **B13** with a carboxylic acid, or an acid chloride or an isocyanate in the presence of an apprpropriate coupling agent such as a carbodimide, or base, as needed provides compounds **B10**

Scheme 2



EXAMPLE B10-1

2-{[1-(4-Chloro-phenyl)-2-isopropyl-2,7-diaza-spiro[3.5]nonane-7-carbonyl]-amino}-3-methyl-pentanoic acid methyl ester



Step A: Preparation of 1,1-Dimethylethyl 1-oxo-3-(4-chlorophenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (*B5-1*)

In a dry 250 mL, 3-necked flask, add 4-chlorobenzaldehyde (6.51 g) and dry THF (20 mL) and cool to -30 C. Add 1M lithium bis(trimethylsilyl)amide in THF (47 mL) dropwise keeping the temperature at ~ 30 C. Then, warm the reaction mixture to 0 C for 30 min. (Solution A)

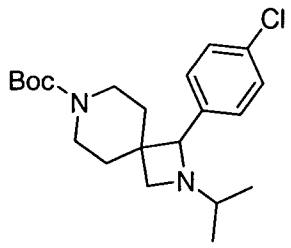
In a dry 250 mL flask, under a nitrogen atmosphere, add diisopropylamine (6.1 mL) and dry THF (10 mL) and cool to 0 C. Add 2.5 M n-butyl lithium in hexane (17.4 mL, 43.5 mmole) dropwise and let stir at -60 C for 25 min. Then, add a solution of

ethyl 1-tert-butoxycarbonylpiperidine-4-carboxylate (*1*) (9.3 g) in dry THF (10 mL) dropwise maintaining the temperature at -65 to -55 C for 90 min. (Solution B) Add solution A to solution B dropwise maintaining temperature at -55 to -65 C for 2.5 h. Warm to RT and stir overnight. Quench with sat. NH4Cl (50 mL) dropwise at 25-30 C. Partition with EtOAc. Concentrate the dried (MgSO4) EtOAc solution in vacuo to give an amber foam (14.72 g). Dissolve the amber foam in EtOAc (15 mL) at ~55 °C. Add hexane (3 x 10 mL) and let stand overnight. Collect the crystals and dry in a vacuum oven to give the title compound as a yellow solid (7.67 g).

Step B: Preparation of 1,1-Dimethylethyl 1-oxo-3-(4-chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (*B7-1*)

In a dry 100 mL 3-necked flask, add 1,1-dimethylethyl 1-oxo-3-(4-chlorophenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (7.0 g) and dry DMF (50 mL) and cool to ~2 C. Add portionwise sodium hydride in 60% oil dispersion (1.10 g) keeping temperature at 2-5 C. After 5 min., add portionwise 2-bromopropane (2.6 mL) keeping temperature 3 to 8°C. Warm mixture to 50°C. After 4.5 h, cool to ~20 °C and add ice water (400 mL). Extract with EtOAc (2 x 499 mL). Extract EtOAc with brine (50 mL). Concentrate the dried ($MgSO_4$) EtOAc in vacuo to give the title compound as an amber oil (8.80 g). Add EtOAc : hexane (1:2, 20 mL) and keep overnight at RT to give the title compound as a yellow solid (5.75 g).

Step C: Preparation of 1,1-Dimethylethyl 1-(4-chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (*B8-1*)



B8-1

Under a nitrogen atmosphere, in a dry 500 mL 3-necked flask, add $LiAlH_4$ (0.87 g) and THF (dried over Mol sieves) (96 mL) and cool to 10 C (ice bath). Add $AlCl_3$ (3.33 g) portionwise keeping the temperature at ~10 C. Heat to 50 – 60 C for 30 min., then cool to -40 to -50 C. Add 1,1-dimethylethyl 1-oxo-3-(4-chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (5.75 g in dry THF (150 mL). Warm the

reaction mixture to -20 C and monitor at 15 min intervals until starting material is gone (~ 60 min.). At -30 C, quench the reaction mixture at ~ -30 C with 10% NaOH, then warm to room temperature. Extract with diethyl ether (2 x 300 mL). Extract the diethyl ether with brine. Concentrate the dried ($MgSO_4$) Et2O in vacuo to give the title compound as a viscous oil (9.79 g). Add EtOAc (5 mL) and hexane (25 ml) and let stand at RT to give the title compound as a white solid (.031 g). Filtrate (4.47 g) in EtOAc (30 mL) and hexane (30 mL) gave additional compound (3.56 g) which was placed on an Analogix system: Column of silica gel (115 g) and eluted with hexane / EtOAc, 20 mL fractions collected. Concentration of fraction 54-145 gave the title compound (2.94 g) as a white solid.

Step D: Preparation of 1-(4-Chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]nonane (*B9-1*)

Under a nitrogen atmosphere, treat 1,1-dimethylethyl 1-(4-chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (2.74 g) in dry CH2Cl2 (10 mL) with trifluoroacetic acid (2 x 5 mL) at RT for 45 min. Concentrate the reaction mixture in vacuo. Add CH_2Cl_2 (10 mL) and concentrate in vacuo (three times) to give a viscous colorless oil (5.76 g). Partition this oil between CH_2Cl_2 and 1N NaOH. Concentrate the dried ($MgSO_4$) CH_2Cl_2 solution in vacuo to give the title compound (1.37 g) as a viscous oil.

Step E: Preparation of N-[[1-(4-Chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]non-7-yl]carbonyl]-L-Isoleucine, Methyl Ester, Hydrochloride (*B10-1*)

Treat 1-(4-Chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]nonane (0.068 g) in $ClCH_2CH_2Cl$ (2 mL) with (2S,3S)-2-isocyanato-3-methylvaleric acid, methyl ester (70 uL), and the resulting mixture stirred at RT for 48 h. P-S Trisamine (Argoonaut, 4.64 mmol/g) (250 g) and $ClCH_2CH_2Cl$ (2 mL) were added and the resulting mixture was shaken to 20 h. The reaction mixture was filtered, the resin washed with CH_2Cl_2 (2 mL). The resulting filtrate was concentrated in vacuo and then placed on a silica gel plate (1000 u) and eluted with CH_2Cl_2 : MeOH (95:5) to give of N-[[1-(4-chlorophenyl)-2-isopropyl-2,7-diazaspiro[3.5]non-7-yl]carbonyl]-L-Isoleucine, white residue (0.0464 g). Add MeOH (1 mL) and 0.1N HCl in MeOH (2 mL), and concentrate in vacuo to give the title compound, as a white solid (0.0408 g).

Procedure for the preparation of B5-2, B5-3, and B5-4

Using essentially the same procedure as Step A above, with the appropriate aldehydes, provides the following compounds:

B5-2 R3=Phenyl

^{1}H NMR (300MHz, DMSO) – δ7.4(d, 2H), 7.3(br, 3H), 4.6(s, 1H), 3.5(br, 2H), 3.2(br, 1H), 3.0(br, 1H), 1.9(br, 2H), 1.3(s, 9H), 1.2(br,1H), 1.0(br,1H)

B5-3 R3= 2-Pyridyl

^{1}H NMR (300MHz, CDCl3)

δ8.7(d, 1H), 7.8(t, 1H), 7.4(d, 1H), 7.2(m, 1H), 6.2(s,1H), 4.5(s, 1H), 3.8(br, 1H), 3.6(m, 1H), 3.2(br, 2H),2.1(br,1H), 1.9(m,1H),1.5(m,1H), 1.4(s,9H), 1.1(m,1H)

B5-4 R3=3-Pyridyl

^{1}H NMR (300MHz, CDCl3) –

δ8.2(d, 2H), 7.3(d, 1H), 7.0(m, 1H), 4.2(s, 1H), 3.3(br,1H), 3.2(t, 1H), 3.1(br, 1H), 3.0(br, 1H), 1.9(d, 1H),1.6(t,1H), 1.1(s,10H),0.8(m,1H)

Preparation of B7-2

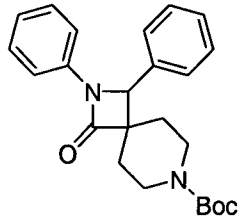
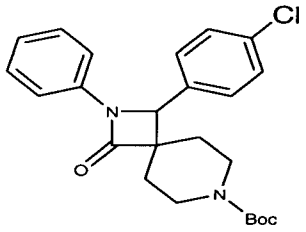
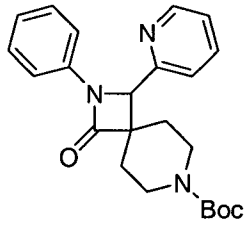
R^3 = Phenyl, R^1= Phenyl

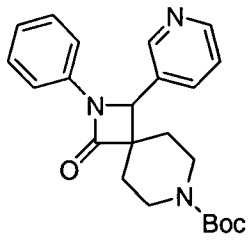
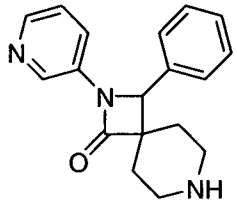
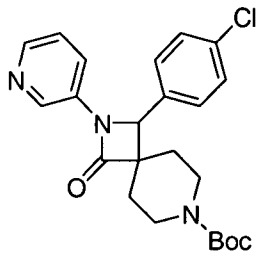
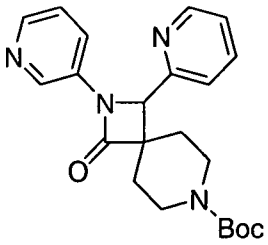
To a stirred solution of lactam (**B5-2**, 94mmole) in dioxane (200ml), bromobenzene (24g, 104mmole) and N,N-dimethylethylenediamine (1.1ml, 9.4 mmole), CuI (3.6g, 18mmole) and K_2CO_3 (26g, 188mmole) were added. The reaction mixture was refluxed over night. After cooling to room temperature, the solid was removed by filtration and the organic layer was diluted with ethyl acetate (1L), washed with brine,dried over $MgSO_4$ and concentrated to give a solid which was obtained by filtration, washed with ethyl acetate to give the title compound (Y: 92%)

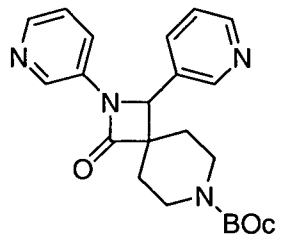
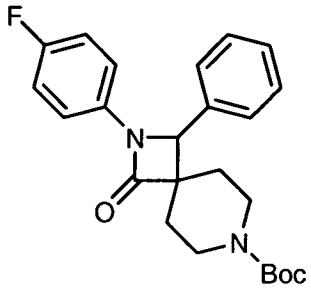
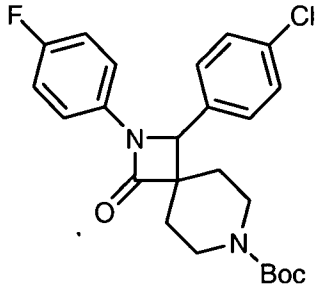
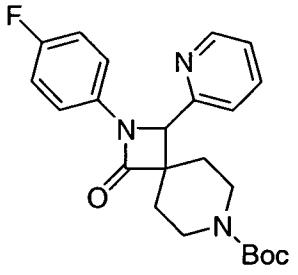
Using essentially the same procedures as above and the appropriate reagents as needed depending upon the R^2 and R^1 groups, provided the compounds in Table 9 below with the reaction yield and purification method noted. (When R^1 is aryl or heteroaryl the preferred method is as described for the preparation of B7-2 and when

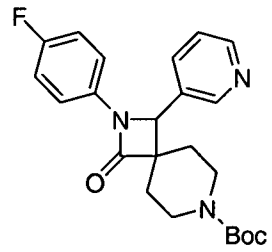
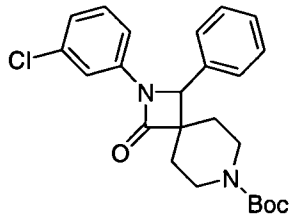
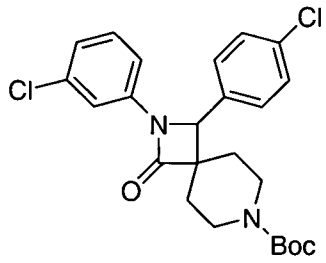
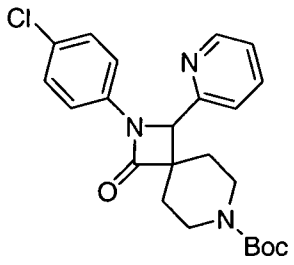
R^1 is alkyl or substituted alkyl the preferred method is as described for the preparation of B7-1.

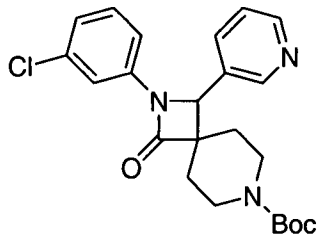
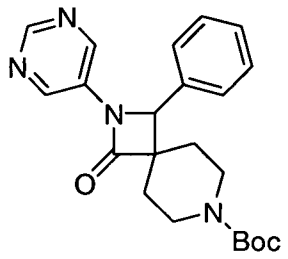
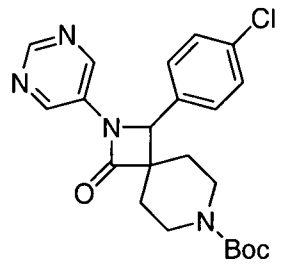
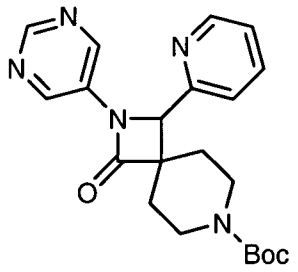
Table 9

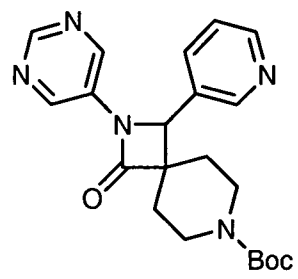
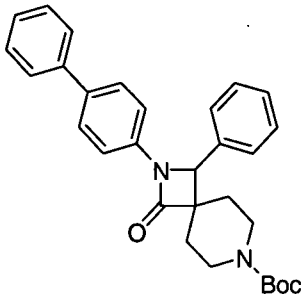
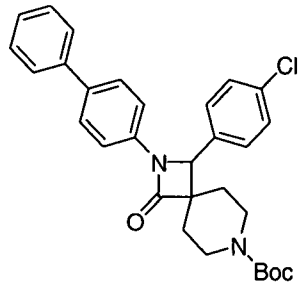
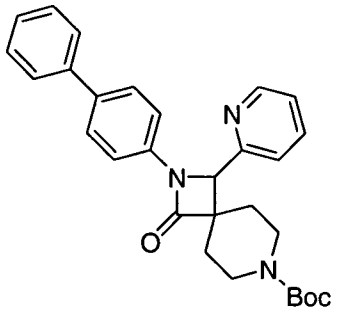
Structure	Yield	Purification
	90%	Recrystallization Hex:Ether(1:2)
	90%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether(1:2)

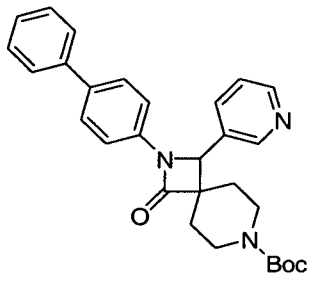
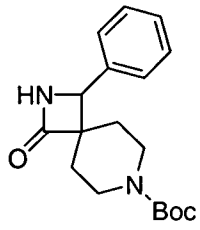
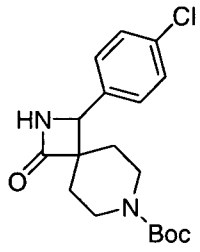
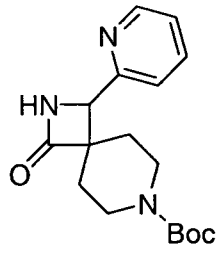
	80%	Recrystallization Ether
	80%	Recrystallization Ether
	80%	Recrystallization Ether
	75%	Recrystallization Hex:Ether(1:2)

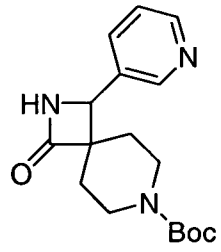
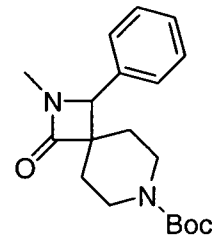
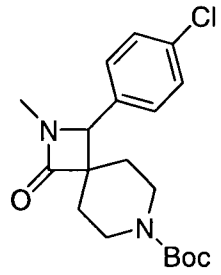
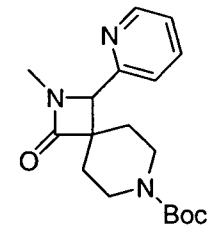
	74%	Recrystallization Hex:Ether
	91%	Recrystallization Ether
	92%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether

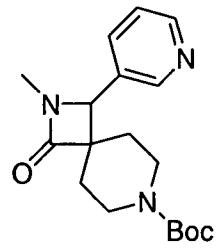
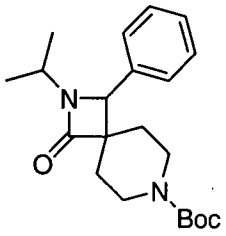
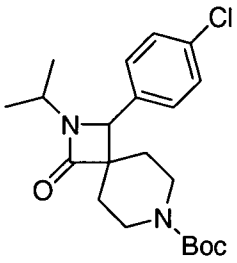
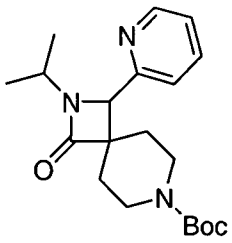
	85%	Recrystallization Ether
	88%	Recrystallization Hex:Ether(1:2)
	92%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Ether

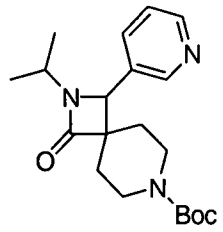
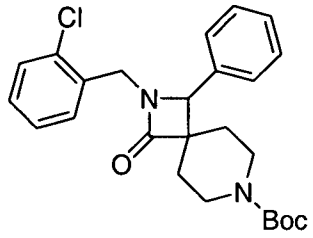
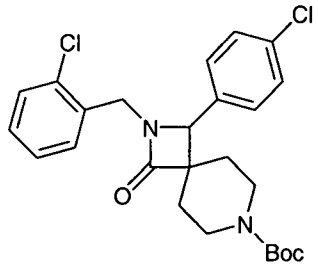
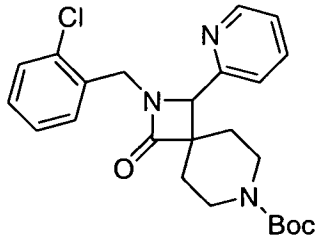
	85%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Ether
	85%	Recrystallization Hex:Ether
	85%	Recrystallization Hex:Ether(1:2)

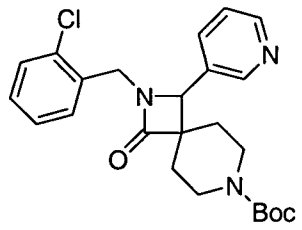
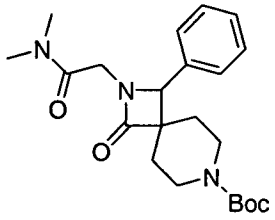
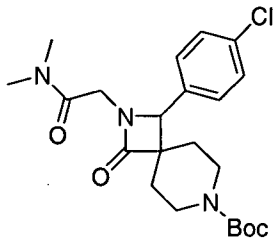
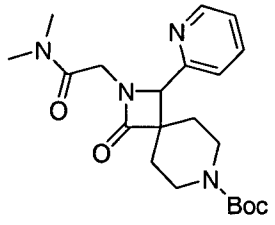
	85%	Recrystallization Ether
	85%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Hex:Ether(1:2)

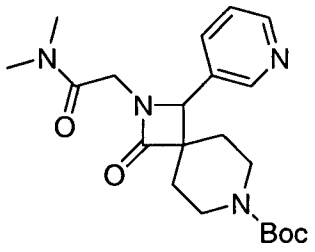
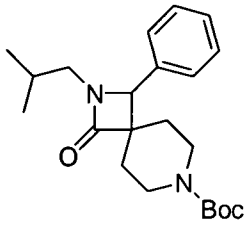
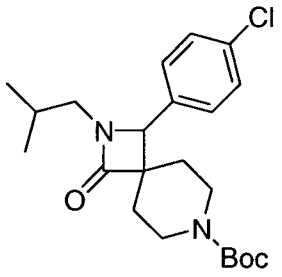
	85%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Hex:Ether(1:2)
	70%	Recrystallization Hex:Ether(1:2)

	70%	Recrystallization Hex:Ether(1:2)
	90%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Hex:Ether(1:2)
	85%	Recrystallization Hex:Ether(1:2)

	85%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether(1:2)

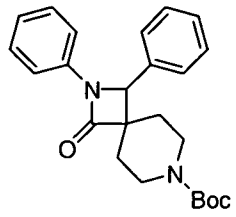
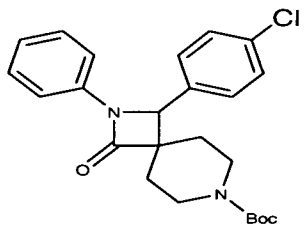
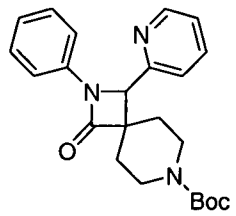
	87%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether(1:2)
	83%	Recrystallization Ether

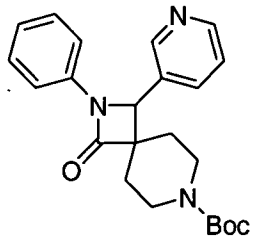
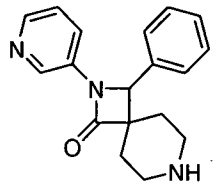
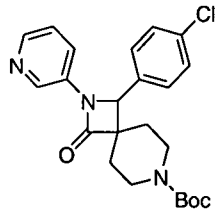
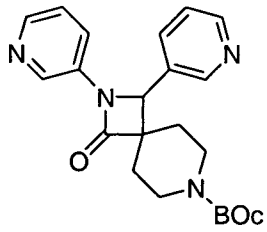
	85%	Recrystallization Hex:Ether
	70%	Recrystallization Hex:Ether(1:2)
	76%	Recrystallization Hex:Ether(1:2)
	75%	Recrystallization Ether

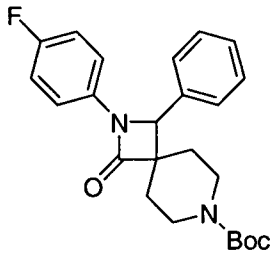
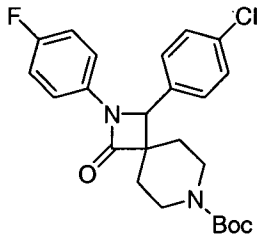
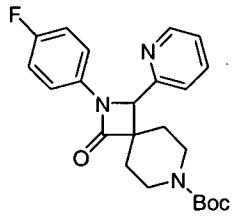
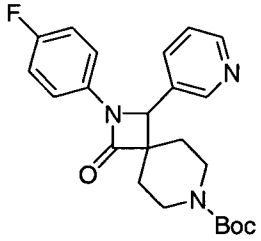
	78%	Recrystallization Ether
	85%	Recrystallization Hex:Ether(1:2)
	80%	Recrystallization Hex:Ether(1:2)

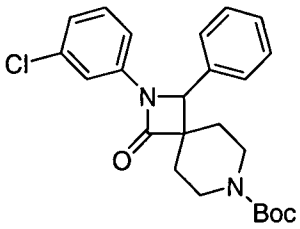
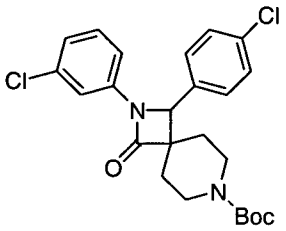
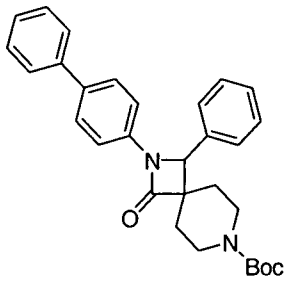
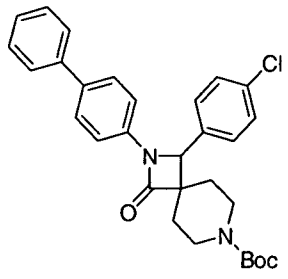
Treatment of the compounds from Table 9, using the conditions for the conversion of **B7-1** to **B9-1**, provided the counterpart compounds wherein the =O group was removed (by reduction with LAH/$AlCl_3$) and the BOC group was removed (by treatment with TFA). The % yield of the reduced product obtained by the reduction of the starting material and the method of purification of the reduced product, as well as the % yield of the decarboxylated product and the purification method of the decarboxylated product is outlined in Table 10.

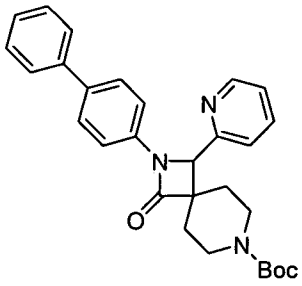
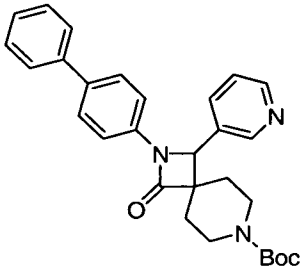
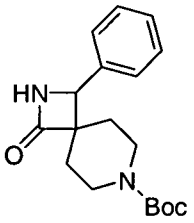
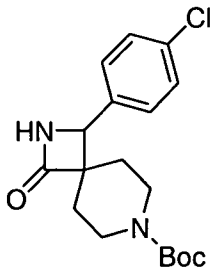
Table 10

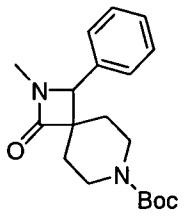
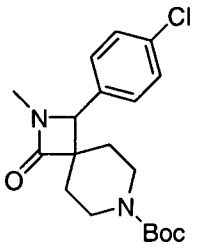
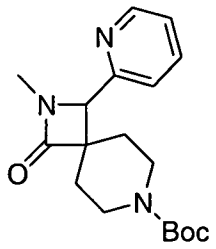
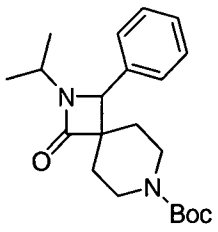
Starting Material From Table 9	Reduction with $LAH/AlCl_3$		Treatment Of Reduced Product With TFA To Yield Decarboxylated Product
	Yield Of Reduced Product	Purification Of Reduced Product	% Yield Of Decarboxylated Product and Purification Method
	65%	Silicagel column (Hex:E.A=3:1)	90% Washed(ether) TFA salt
	65%	Silicagel column (Hex:E.A=3:1)	90% Washed(ether) TFA salt
	45%	Silicagel column (Hex:E.A=2:1)	92% Washed(ether) TFA salt

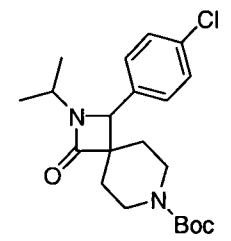
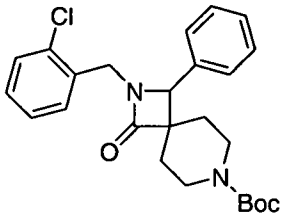
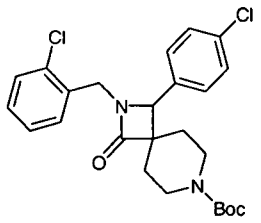
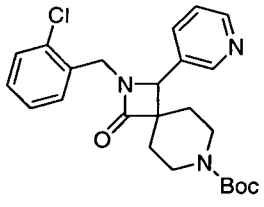
	48%	Silicagel column (Hex:E.A=1:1)	91% Washed(ether) TFA salt
	50%	Silicagel column (Hex:E.A=2:1)	88% Washed(ether) TFA salt
	60%	Silicagel column (Hex:E.A=2:1)	87% Washed(ether) TFA salt
	40%	Silicagel column (Hex:E.A=1:1)	85% Washed(ether) TFA salt

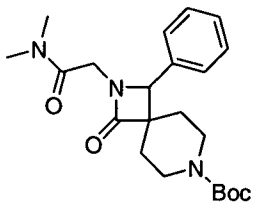
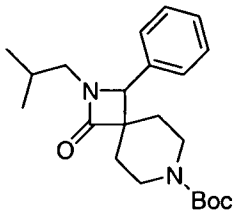
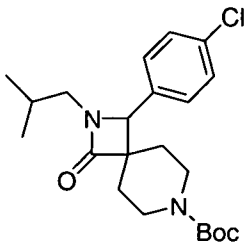
	60%	Silicagel column (Hex:E.A=3:1)	83% Washed(ether) TFA salt
	55%	Silicagel column (Hex:E.A=3:1)	90% Washed(ether) TFA salt
	45%	Silicagel column (Hex:E.A=2:1)	90% Washed(ether) TFA salt
	62%	Silicagel column (Hex:E.A=2:1)	91% Washed(ether) TFA salt

	60%	Silicagel column (Hex:E.A=3:1)	91% Recrystallizaton TFA salt
	65%	Silicagel column (Hex:E.A=3:1)	89% Washed(ether) TFA salt
	50%	Silicagel column (Hex:E.A=3:1)	90% Washed(ether) TFA salt
	68%	Silicagel column (Hex:E.A=5:1)	92% Washed(ether) TFA salt

	60%	Silicagel column (Hex:E.A=3:1)	92% Washed(ether) TFA salt
	65%	Silicagel column (Hex:E.A=3:1)	86% Washed(ether) TFA salt
	60%	Silicagel column (Hex:E.A=3:1)	88% Washed(ether) TFA salt
	48%	Silicagel column (Hex:E.A=2:1)	89% Washed(ether) TFA salt

	60%	Silicagel column (Hex:E.A=3:1)	94% Washed(ether) TFA salt
	65%	Silicagel column (Hex:E.A=3:1)	90% Washed(ether) TFA salt
	60%	Silicagel column (Hex:E.A=1:1)	86% Washed(ether) TFA salt
	65%	Silicagel column (Hex:E.A=5:1)	91% Washed(ether) TFA salt

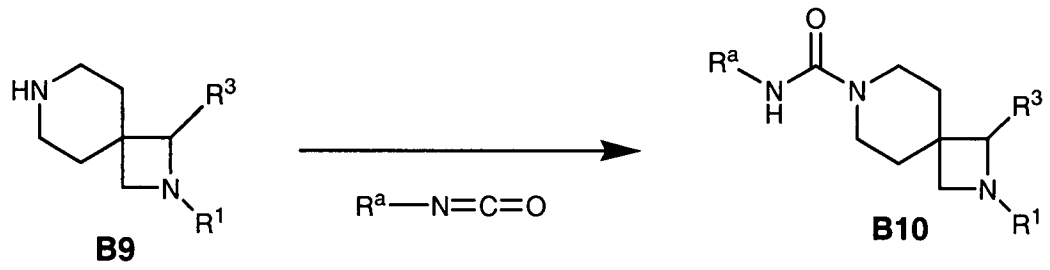
	70%	Silicagel column (Hex:E.A=5:1)	92% Washed(ether) TFA salt
	65%	Silicagel column (Hex:E.A=5:1)	85% Washed(ether) TFA salt
	62%	Silicagel column (Hex:E.A=5:1)	86% Washed(ether) TFA salt
	70%	Silicagel column (Hex:E.A=3:1)	90% Washed(ether) TFA salt

	48%	Silicagel column (Hex:E.A=2:1)	91% Washed(ether) TFA salt
	70%	Silicagel column (Hex:E.A=3:1)	92% Washed(ether) TFA salt
	62%	Silicagel column (Hex:E.A=3:1)	92% Washed(ether) TFA salt

The compounds prepared according to Table 10 can be converted to the corresponding free bases by the addition of NaOH and extraction with DCM.

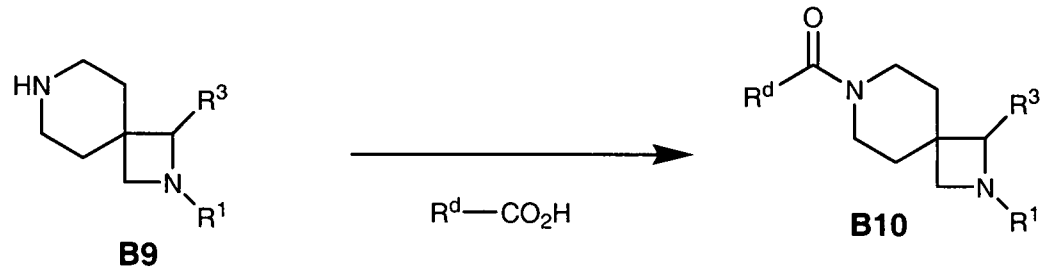
Compounds of formula **B9** can be converted into compounds **B10** using the general procedures provided below:

General method for the preparation of tertiary urea compound libraries



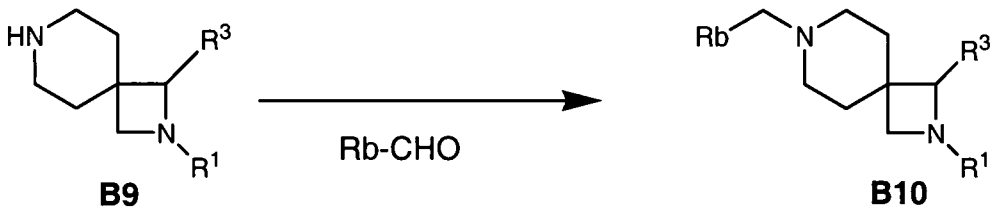
To a solution of compound **B9** (0.025 mmol) in DCE/MeOH (25:1 v/v, 1 mL) was added a 0.5 M solution of isocyanate (0.075 mmol) in DCE. The reaction mixture was agitated at room temperature for 20 hours. Dichloroethane (0.5 mL), polystyrene isocyanate resin (0.057 g, 0.087 mmol) and polystyrene trisamine resin (0.049 g, 0.207 mmol) were added. The reaction mixture was agitated at room temperature for 16 hours. The reaction product was filtered and the resin was washed with acetonitrile (0.5 mL). The organic solvent was evaporated under reduced pressure to yield the desired compound of formula **B10**

General method for the preparation of amide compound libraries



To a mixture of polystyrene EDC resin (0.106 g, 0.146 mmol) and a compound of type **B9** (0.025 mmol) in MeCN/THF (3:1 v/v, 1 mL) was added a 1 M solution of carboxylic acid (0.038 mmol) in DMF and then a 0.5 M solution of HOBT (0.038 mmol) in MeCN/THF (3:1 v/v, 0.20 mL). The reaction mixture was agitated at room temperature for 20 hours. Acetonitrile (0.5 mL), polystyrene isocyanate resin (0.049 g, 0.075 mmol) and polystyrene trisamine resin (0.035 g, 0.148 mmol) were added. The reaction mixture was agitated at room temperature for 64 hours. The reaction product was filtered and the resin was washed with acetonitrile (0.5 mL). The organic solvent was evaporated under reduced pressure to yield the desired compound **B10** which was characterized by LCMS.

General method for the preparation of N-alkyl compound libraries

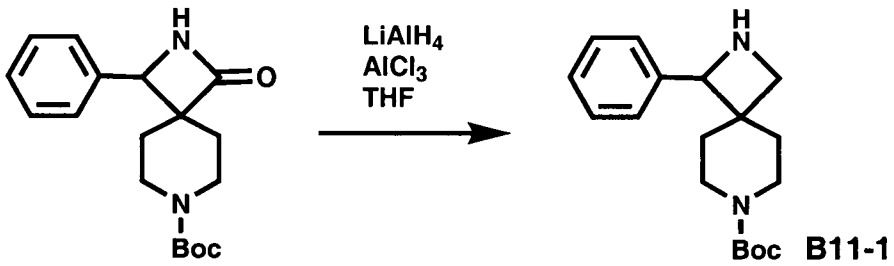


B9 **B10**

To a solution of compound **B9** (0.025 mmol) in DMF/THF (1:1 v/v, 1 mL) was added a solution of the appropriate aldehyde (0.075 mmol) in DCE followed by addition of sodium triacetoxyborohydride (3 equivalents). The reaction mixture was agitated at room temperature for ~20 hours. MeOH (0.5 mL) was added to each cartridge, and shaken for 10 mins or until the evolution of gas stopped. MP-TsOH resin (~100 mg) was added to the reaction vessel , and shaken for 1-2 hrs. The solvent was then removed by filtration and the resin washed with DCE (3x), then with methanol (3x) and the desired products eluted off the resin by stirring with with 2N ammonia in methanol (1.5-2 ml, for 1 h) and filtration.The organic solvent was evaporated under reduced pressure to yield the desired compound **B10** which was characterized by LCMS.

EXAMPLE B11-1

Preparation of 1,1-Dimethylethyl 1-phenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate



B11-1

Under an argon atmosphere, place lithium aluminum hydride 5.3 g) in a dry 250 mL RB 3-necked flask. Add diethyl ether (molecular sieves) (100 mL). Cool mixture to 0° C, and add aluminum chloride (5.97 g) portionwise maintaining temperature at -5° to 5°. Stir the resulting mixture for 30 min. Under argon, filter this mixture into a nitrogen purged 1 liter RB 3-necked flask. Wash the cake with dry diethyl ether (100

mL). Cool the filtrate to -45° C, and add 1,1-dimethylethyl 1-oxo-3-(4-chlorophenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (8.40 g) in dry (molecular sieve) THF (300 mL) dropwise maintaining the temperature at -40° to -45° C. Warm the mixture slowly to -20° C (-25° to -18°), and monitor an aliquot quenched with 2.5N NaOH by TLC on silica gel using CH_2Cl_2:MeOH 9:1 as eluant. After 2 h, cool the reaction mixture to -30° C and slowly quench 10 % NaOH (temperature to -5° C). Extract the reaction mixture with diethyl ether (2 x 400 mL). Extract the ether solution with brine, and concentrate the ($MgSO_4$) ether solution in vacuo to give a white foam. Chromatograph this foam on flash silica gel (650 mL) with MeOH : CH2Cl2: 2.5:97.5 (3 L); 5:95 (5 L); 10:90 (2 L). Collect 500 mL fractions (1-6), then 250 mL fractions. Concentrate fractions 3 to 6 to give starting compound (6.46 g), and fractions 11-27 to give the title compound as an amber residue (0.4995 g).

Compound **B11** can be converted to compounds of formula **B10** according to Scheme 2, using the procedures described in Steps 3, 5 and 6 in Scheme 1, as appropriate for the conversion of **B8** into **B9** and **B10.**

ASSAYS

Methods for Evaluating Functional Effects on Ion Channels

Functional evaluation of voltage-gated ion channels was used to determine potency and/or single concentration efficacy of proprietary compounds. Two different methodologies were used to measure ion currents: the IonWorks HT (Molecular Devices, Sunnyvale, CA) a moderate throughput voltage clamp screening platform that utilizes 96-well compound plates and conventional whole cell patch clamp for lower throughput, higher fidelity determinations.

Cell Lines

HEK cells were transiently transfected and then selected for stable heterologous expression of different channel proteins of interest. Calcium channel cell lines expressed a resting potassium current, human $K_{ir}2.1$, and the pore forming α-subunit of voltage-gated calcium channels. In the case of $Ca_V2.1$ cells the auxiliary subunit, β_2a, was also expressed. Calcium channel lines that were used to generate the data in this document expressed either human $Ca_V3.2$, rat $Ca_V3.2$ or human $Ca_V2.1$. The human heart sodium channel, $hNa_V1.5$, was stably expressed in CHO cells. These cells were licensed from the University of Pennsylvania.

Cell lines were grown at 37 °C in humidified incubators, equilibrated with 95% air / 5% CO_2. CHO cells were grown in Ham's F-12 medium. HEK cells were grown in DMEM. All media were supplemented with 10% heat-inactivated fetal bovine serum, penicillin, streptomycin and appropriate selection antibiotics (zeocin, geneticin and/or hygromycin). Cells were passaged when 80% confluent or less.

IonWorks Screen for hCaV3.2

The extracellular buffer for experiments using this instrument contained the following (mM) (NaCl 125, HEPES 10, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.8, 0.2 $BaCl_2$ pH 7.35). The IonWorks uses amphotericin to gain electrical access to the cell interior. The internal solution contained (mM concentrations): 130 K-gluconate, 20 KCl, 5 HEPES-KOH (pH 7.25), 2 $CaC1_2$, 1 $MgCl_2$. Amphotericin added at 5 mg in 65 ml when present (in 650 µl DMSO). All internal and external solutions for this experiment contain 1% DMSO. Cells were acutely trypsinized from a T-75 flask and resuspended in extracellular buffer at a density of $2X10^5$ cells/ml.

Experiments were performed at room temperature. Transmembrane potential was held at -100 mV for 5 seconds prior to running the voltage protocol. During this time leak currents were measured during a step to -110 mV (200 milliseconds). T-type calcium currents were activated with a 250 millisecond step to -20 mV. This depolarization step was repeated for a total of 10 pulses with an interpulse interval of 1 second. Data were excluded if the following acceptance criteria were not met: total resistance for the pre-compound scan > 65 MΩ, pre-compound current > 250 pA, post compound total resistance > 50 MΩ.

T-type currents were measured as the peak inward current minus the current at the end of the 250 msec step to -20 mV. After the recoding configuration was established there was a pre-compound measurement of current amplitude. Compound was added as a 3X solution containing 1% DMSO. After incubation with compound for 10 minutes currents were measured again. The current amplitude after compound addition was divided by the pre-compound current for pulse 10 to determine the fraction of current remaining after compound addition. For each compound, 8-point concentration-effect relationships were measured with ½ log serial dilutions. These data were then transferred into GraphPad Prism (v 4) and non-linear regression analysis was used to estimate the IC_{50} for each test compound.

Conventional Whole Cell Patch Clamp

Cells were plated onto 9 mm diameter circular coverglass in the appropriate growth medium and placed in a 37 °C incubator until used. Whole cell patch clamp studies were conducted at room temperature using conventional methods. PCLAMP software (v8 or 9) was used n conjunction with a compatible A/D D/A board, a Pentium III personal computer and either a Multiclamp 700 or an AxoPatch 1D amplifier was used to generate voltage clamp protocols, acquire data and measure currents.

At the time of study, a piece of coverglass with attached cells was transferred to a recording chamber on the stage of an inverted microscope and the whole cell configuration of patch clamp was established. The recording chamber was gravity perfused with extracellular solution at a flow rate of approximately 3 ml/min. Patch electrodes had resistances of 2-3 MΩ when filled with pipette solution. The extracellular solution was a HEPES-buffered saline (149 NaCl, 10 HEPES-NaOH (pH 7.4), 10 glucose, 5 CsCl, 2 $MgCl_2$, 5 $CaCl_2$; concentrations in mM). The pipette solution contained (mM concentrations) (115 CsCl, 10 HEPES-CsOH (pH 7.3), 4 MgATP, 10 EGTA; osmolarity to 310 mM with sucrose). All solutions contained 0.1% DMSO.

The holding potential was –100 mV for all protocols. Interpulse interval was 15 seconds. The time course of $hCa_V3.2$ or $rCa_V3.2$ current was examined with a 200 millisecond test pulse to -35 mV. $Ca_V3.2$ currents were measured as the peak current 10-30 milliseconds after the voltage was stepped to -35 mV. P/N 4 leak subtraction was used. The amplifier low pass filter was set to 10 kHz and the data were sampled at 10 kHz. Data were filtered offline with a Gaussian filter with a -3 dB cutoff of 280 Hz. The voltage protocol for hCaV2.1 currents differed only in terms of the voltage for the depolarizing test potential. For $hCa_V2.1$ currents were activated with a 200 millisecond step to 0 mV. $hCa_V2.1$ currents were measured from the leak-subtracted traces as the average current between 190 and 200 milliseconds after the step to 0 mV. The voltage protocol for sodium currents included a 150 millisecond hyperpolarizing pulse to -140 mV to optimize channel availability, followed by a 20 millisecond test pulse to -20 mV. Sodium currents were measured from leak subtracted traces as the peak transient inward current.

All drug effects were measured after a steady-state effect was achieved. Concentration-effect relationships were derived by exposing each cell to only a single

concentration of test article. For non-linear regression analysis the post-compound current amplitude was normalized to the pre-compound current amplitude for each cell. If a given current was inhibited by >50% at a concentration of 10 μM or less, the data for multiple concentrations of compound and corresponding vehicle and time control cells were entered into GraphPad Prism (v 4) for non-linear regression analysis to determine the IC_{50}.

Pain

The actions of the compounds of formula I for the treatment or prevention of pain may be assessed by various animal models, for example, by the following tests:

(1) Formalin test: Mice are gently restrained and 30 μl of formalin solution (1.5% in saline) is injected subcutaneously into the plantar surface of the right hind paw of the mouse, using a microsyringe with a 27 gauge needle. After the formalin injection, the mouse is immediately put back into the Plexiglas observation chamber (30 x 20 x 20 cm) and the nociceptive response of the animal to formalin injection is observed for a period of 60 min. The duration of licking and flinching of the injected paw is recorded and quantified every 5 min for the total observation period. The recording of the early phase (first phase) starts immediately and lasts for 5 min. The late phase (second phase) starts about 10-15 min after formalin injection.

(2) L5 and L6 spinal nerve ligation of the sciatic nerve (neuropathic pain model): The peripheral neuropathy is produced by ligating the L5 and L6 spinal nerves of the right sciatic nerve, based on the method previously of Kim and Chung (1992). Briefly, rats are anaesthetized with chloral hydrate (400 mg/kg, i.p.), placed in a prone position and the right paraspinal muscles separated from the spinous processes at the L4-S2 levels. The L5 transverse process is carefully removed with a small rongeur to identify the L4-L5 spinal nerves. The right L5 and L6 spinal nerves are isolated and tightly ligated with 7/0 silk thread. A complete hemostasis is confirmed and the wound sutured.

(3) Chronic constriction injury (CCI) of the sciatic nerve (neuropathic pain model): Surgery is performed according to the method described by Bennett & Xie (1987). Rats are anaesthetized with chloral hydrate (400 mg/kg, i.p.) and the common sciatic

nerve is exposed at the level of the mid-thigh. Proximally, at about 1 cm from the nerve trifurcation, four loose ligatures (4/0 silk) spaced 1 mm are tied around the nerve. The ligature delays, but does not arrest, circulation through the superficial epineural vasculature. The same procedure is performed except for ligature placement (sham surgery) in a second group of animals.

(4) Carrageenan (inflammatory pain model): The right hind paw of each animal is injected at subplantar level with 0.1 mL of carrageenan (25 GA needle). Pre-tests are determined prior to carrageenan or drug administration. In the POST-TREATMENT protocol, rats are tested 3 hours after carrageenan treatment to establish the presence of hyperalgesia and then at different times after drug administration. In the PRE-TREATMENT protocol, one hour after drug administration, rats are treated with carrageenan and they are tested starting from 3 hours later.

(5) Freund's adjuvant-induced arthritic model (inflammatory pain model): Animals receive a single subplantar injection of 100 mL of a 500 mg dose of heat-killed and dried Mycobacterium tuberculosis (H37 Ra, Difco Laboratories, Detroit, MI, USA) in a mixture of paraffin oil and an emulsifying agent, mannide monooleate (complete Freund's adjuvant). Control animals are injected with 0.1 mL mineral oil (incomplete Freund's adjuvant).

(6) Measurement of tactile allodynia (behavioral test): Behavioral tests are conducted by observer blinded to the treatment during the light cycle to avoid circadian rhythm fluctuation. Tactile sensitivity is evaluated using a series of calibrated Semmes-Weinstein (Stoelting, IL) von Frey filaments, bending force ranging from 0.25 to 15 g. Rats are placed in a transparent plastic box endowed with a metal mesh floor and are habituated to this environment before experiment initiation. The von Frey filaments are applied perpendicularly to the midplantar surface of the ipsilateral hind paws and the mechanical allodynia is determined by sequentially increasing and decreasing the stimulus strength ("*up-down*" paradigm of the filament presentation). Data are analysed with a Dixon non-parametric test (Chaplan et al. 1994). Paw licking or vigorously shaking after stimulation is considered pain-like responses.

(7) Thermal hyperalgesia (behavioral test): Thermal hyperalgesia to radiant heat is assessed by measuring the withdrawal latency as an index of thermal nociception (Hargreaves *et al.*, 1998). The plantar test (Basile, Comerio, Italy) is chosen because of its sensitivity to hyperalgesia. Briefly, the test consists of a movable infrared source placed below a glass plane onto which the rat is placed. Three individual perspex boxes allow three rats to be tested simultaneously. The infrared source is placed directly below the plantar surface of the hind paw and the paw withdrawal latency (PWL) is defined as the time taken by the rat to remove its hind paw from the heat source. PWLs are taken three times for both hind paws of each rat and the mean value for each paw represented the thermal pain threshold of rat. The radiant heat source is adjusted to result in baseline latencies of 10-12 sec. The instrument cut-off is fixed at 21 sec to prevent tissue damage.

(8) Weight bearing (behavioral test): An incapacitance tester is employed for determination of hind paw weight distribution. Rats are placed in an angled plexiglass chamber positioned so that each hind paw rested on a separate force plate. The weight bearing test represents a direct measure of the pathological condition of the arthritic rats without applying any stress or stimulus, thus this test measures a spontaneous pain behaviour of the animals.

GPR119 Screening Assay:

Reagent Preparation:

Stimulation Buffer: 100ml HBSS (GIBCO # 14025-092)
+ 100mg BSA (MP Biomedicals faction V, #103703) = 0.1%
+ 500ul 1M HEPES (Cellgro #25-060-CI) = 5mM
+ 75ul RO-20 (Sigma B8279; 20mM stock in DMSO stored in aliquots at -20C) = 15uM
(made fresh daily)

B84 (N-[4-(methylsulfonyl)phenyl]-5-nitro-6-[4-(phenylthio)-1-piperidinyl]-4-pyrimidinamine, see WO 2004/065380): A 10mM stock solution of the test compound in DMSO was prepared, aliquoted and stored at -20C. For Totals - Dilute 1:33.3 in DMSO then 1:50 in Stimulation Buffer = 6uM in 2%DMSO(= 3uM B84 and 1%DMSO final). For Dose Response Curve – 3ul stock + 7ul DMSO + 490ul Stim Buffer = 60uM in 2%DMSO (= 30uM B84 and 1% DMSO final). (made fresh daily).

Cell Line:

Human clone 3: HEK 293 cells stable transfected with human-SP9215(GPR119)/pcDNA3.1 and also stable for pCRELuc, Stratagene. Cells are maintained in DMEM containing 10%FBS (Invitrogen #02-4006Dk, lot #1272302, heat inactivated), 1x MEM, 1x Pen/Strep, 0.1mg/ml Hygromycin B, and 0.5mg/ml G418. Cells are split 1:8 twice per week.

cAMP Kit: LANCE™ cAMP 384 kit, Perkin Elmer #AD0263

Compound Dilutions:

Add DMSO to vials containing compounds to yield a 1mg/ml solution.

1. Dilute compounds to 60µM in Stimulation buffer. Make ½ log dilutions into Stimulation buffer containing 2%DMSO using the epMotion robot. 10 point dose response curve 1nM to 30uM.
2. Compounds are run in quadruplicate, 2 separate dilutions for each, sets 1 and 1a.

Assay Procedure:

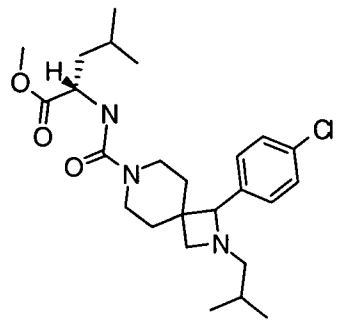
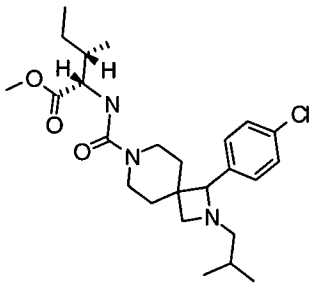
1. The afternoon before the assay, replace the media in the flask of Human clone 3 cells with Optimem. (Gibco # 11058-021) NOTE: cells should be in culture 6-8 days.
2. Next morning, pipet the cells gently off the flask using HBSS (RT).
3. Pellet the cells (1300rpm, 7min, RT) and resuspend in Stimulation Buffer at 2.5x10e6/ml (=5-8,000 cell / 6ul). Add 1:100 dilution of Alexa Fluor 647-anti cAMP antibody (provided in the kit) directly to the cell suspension.
4. Into white 384-well plates (Matrix) add 6ul of 2x B84, cmpds or stim buffer for nsb. They all contain 2% DMSO (= 1%DMSO final).
5. Add 6ul of the cell suspension to the wells. Incubate 30 minutes RT.
6. For the std curve add 6ul cAMP std solution diluted in Stim Buffer + 2%DMSO according to kit directions (1000-3nM). Add 6ul of 1:100 anti-cAMP dilution in Stim Buffer to std wells.
7. Make Detection Mix according to kit instructions and incubate 15 min RT.
8. Add 12ul Detection Mix to all the wells. Mix gently by tapping and incubate 2-3 hrs RT.
9. Read on the Envision under the protocol "Lance/Delphia cAMP"

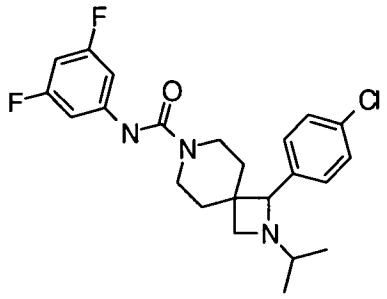
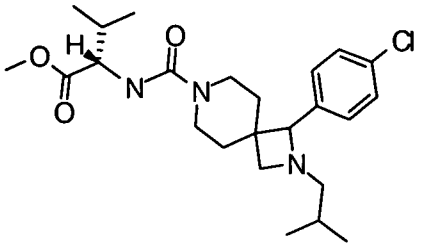
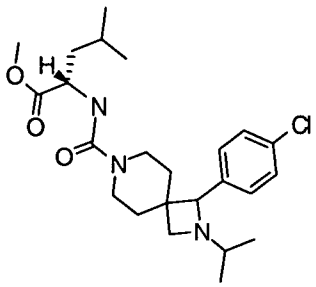
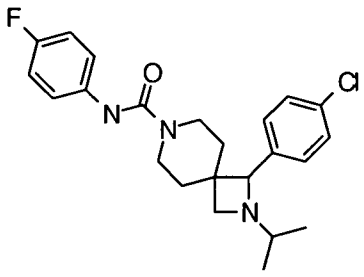
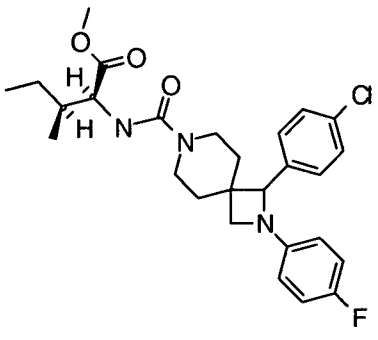
10. Values (nM) for each sample are determined by extrapolation from the std curve. %Control, Fold and EC50 (Control = 3uM B84) are determined for each compound, averaging sets 1 and 1a.

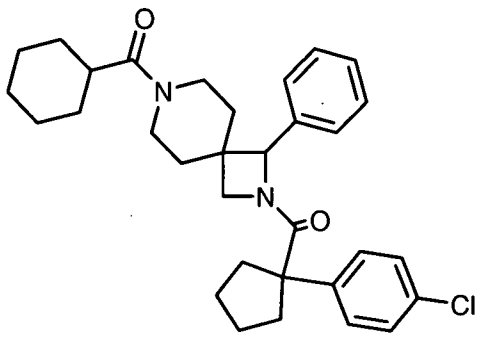
Results

In the Cav3.2 Ionworks assay the IC_{50} of the compounds in Table 5 were within the range of 23 to 23506 nM Table 7 also provides Cav3.2 Ionworks assay data for compounds.

TABLE 7

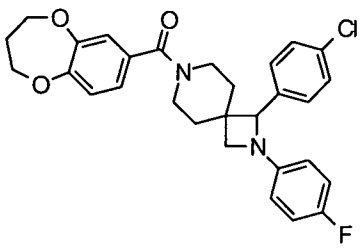
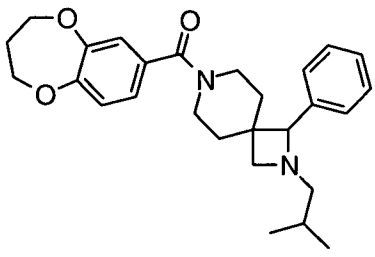
Isomer	Compound	IW hCav3 2 IC50 nM
		23
		26

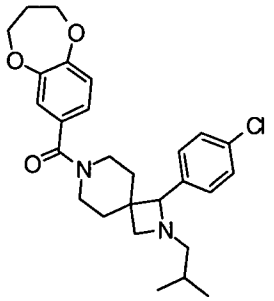
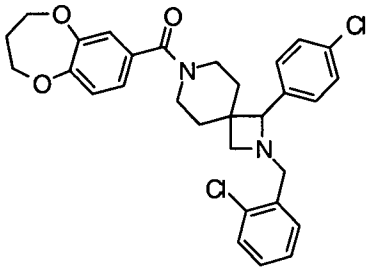
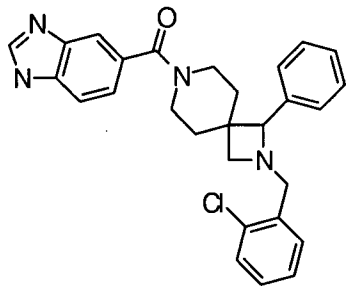
A		32
		32
		65
A		69
		77

		376

In the GPR 119 cAMP assay the IC_{50} activity for the compounds in Table 6 were within the range of: 1640 to 16,260 nM. Table 8 also provides GPR 119 data.

TABLE 8

Compound	GPR 119 cAMP IC50 nM
	1640
	1922

	2620
	2773
	2980

To Measure NPC1L1 The Following Binding Assays Would Be Used:

HEK-293 cells expressing human NPC1L1 can be plated into 384-well black/clear plates (BD Biosciences, Bedford MA) for binding experiments the following day. Cell growth media (DMEM, 10% fetal calf serum, 1 mg/ml geneticin, 100 Units/ml penicillin) can be aspirated. Cell growth media (20 ml) containing 250 nM BODIPY-labeled glucuronidated ezetimibe can be added to each well. Cell growth media (20ml) containing the indicated concentration of compound can then be added to the wells. Unlabeled glucuronidated ezetimibe (100 mM) can be used to determine nonspecific binding. The binding reaction can be allowed to proceed for 4 h at 37C. Subsequently the cell growth media can be aspirated and the cells can be washed once with PBS. The remaining fluorescent labeled glucuronidated ezetimibe bound to the cells can be quantified using a FlexStation plate reader (Molecular Devices,

Sunnyvale CA) to measure fluorescence intensity. Ki values can be determined from competition binding curves (n=4 for each point) using Prism and Activity Base software.

To Measure Inhibition of Cholesterol Absorption The Followinig In Vivo Assay Would Be Used:

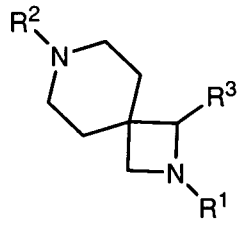
Male rats can be dosed by oral gavage with 0.25ml corn oil or compound in corn oil; 0.5h later, each rat can be given 0.25ml of corn oil orally with 2μCi ^{14}C-Cholesterol, 1.0mg cold cholesterol.

2 h later, the rats can be anesthetized with 100mg/kg IP of Inactin, and a 10ml blood sample can be collected from the abdominal aorta. The small intestine can be removed, divided into 3 sections, and each rinsed with 15ml of cold saline. The rinses can be pooled. The liver can be removed, weighed, and three ~350mg aliquots csn be removed. 5ml 1N NaOH can be added to each intestinal piece, 1ml to each liver aliquot to dissolve at 40º overnight. 2 x 1ml aliquots of the SI digests and the liver digests can be neutralized with 0.25ml 4N HCl and counted. 2 x 1ml aliquots of plasma and intestinal rinses can be counted.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A use of at least one compound of formula (I) for the manufacture of a medicament for treating a disease or condition, wherein said disease or condition is mediated by T-calcium channels, by GPR119 receptors, or by NPC1L1 receptors wherein said compound of formula (I):



(I)

is selected from the group consisting of the compounds defined by Tables 1, 2, 3a, 3b, 3c, 3d and 4a.

2. The use of Claim 1 wherein pain is treated.

3. The use of Claim 2 wherein the pain treated is chronic pain.

4. The use of Claim 2 wherein the pain treated is inflammatory pain.

5. The use of Claim 2 wherein the pain treated is neuropathic pain.

6. The use of Claim 2 wherein the compound of formula I is selected from the group consisting of the compounds in Tables 5 and 7.

7. The use of Claim 1 wherein pain is treated and said method further comprises the administration of at least one additional agent for treating pain.

8. The use of Claim 7 wherein inflammatory pain is treated and said additional agent is an agent for treating inflammatory pain.

9. The use of Claim 7 wherein neuropathic pain is treated and said additional agent is an agent for treating neuropathic pain.

10. The use of Claim 7 wherein said additional agent is selected from the group consisting of: non-opioid analgesics, opioid analgesics steroids, COX-I inhibitors, COX-II inhibitors, agents useful for treating inflammatory bowel disease, and agents useful for treating rheumatoid arthritis.

11. The use of Claim 7 wherein said additional agent is selected from the group consisting of:

non-opioid analgesics selected from the group consisting of: acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusinal, and naproxen;

opioid analgesics selected from the group consisting of: morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone;

steroids selected from the group consisting of: prednisolone, fluticasone, triamcinolone, beclomethasone, mometasone, budisamide, betamethasone, dexamethasone, prednisone, flunisolide and cortisone;

COX-I inhibitors selected from the group consisting of: aspirin and piroxicam;

COX-II inhibitors selected from the group consisting of: rofecoxib, celecoxib, valdecoxib and etoricoxib;

agents useful for treating inflammatory bowel disease selected from the group consisting of: IL-10, steroids, and azulfidine; and

agents useful for treating rheumatoid arthritis selected from the group consisting of: methotrexate, azathioprine, cyclophosphamide, steroids and mycophenolate mofetil.

12. The use of Claim 11 wherein said additional agent is selected from the group consisting of: acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusinal, naproxen, morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone.

13. The use of Claim 10 wherein inflammatory pain is treated and said additional agent is selected from the group consisting of: steroids and non-opioid analgesic agents.

14. The use of Claim 12 wherein neuropathic pain is treated.

15. The use of Claim 2 wherein the compound of formula I is a compound selected from the group of compounds in Table 5.

16. The use of Claim 7 wherein the compound of formula I is a compound selected from the group of compounds in Table 5.

17. The use of Claim 10 wherein the compound of formula I is a compound selected from the group of compounds in Table 5.

18. The use of Claim 2 wherein the compound of formula I is a compound selected from the group of compounds in Table 7.

19. The use of Claim 7 wherein the compound of formula I is a compound selected from the group of compounds in Table 7.

20. The use of Claim 10 wherein the compound of formula I is a compound selected from the group of compounds in Table 7.

21. The use of Claim 1 wherein diabetes is treated.

22. The use of Claim 21 wherein the compound of formula I is selected from the group consisting of the compounds in Table 6.

23. The use of Claim 21 wherein the compound of formula I is selected from the group consisting of the compounds in Table 8.

24. The use of Claim 21 further comprising the administration of at least one additional drug used for the treatment of diabetes.

25 The use of Claim 24 wherein said additional drug is selected from the group consisting of: sulfonylureas, insulin sensitizers, α-glucosidase inhibitors, insulin secretagogues, hepatic glucose output lowering compounds, and insulin.

26. The use of Claim 25 wherein the additiona ldrug is selected from the group consisting of:

sulfonylurea drugs selected from the group consisting of: glipizide, tolbutamide, glyburide, glimepiride, chlorpropamide, acetohexamide, gliamilide, gliclazide, glibenclamide and tolazamide.

PPAR-γ agonists selected from the group consisting of: troglitazone, rosiglitazone, pioglitazone and englitazone;

biguanidines selected from the group consisting of: metformin and phenformin;

DPPIV inhibitors selected from the group consisting of: sitagliptin, saxagliptin, denagliptin and vildagliptin;

PTP-1B inhibitors;

glucokinase activators;

α-Glucosidase inhibitors selected from the group consisting of: miglitol, acarbose, and voglibose;

hepatic glucose output lowering drugs selected from the group consisting of: Glucophage and Glucophage XR;

insulin secretagogues selected from the group consisting of: GLP-1, exendin, GIP, secretin, glipizide, chlorpropamide, nateglinide, meglitinide, glibenclamide, repaglinide and glimepiride; and

insulin selected from the group consisting of: long acting and short acting forms of insulin.

27. The use of Claim 24 wherein the compound of formula I is selected from the group consisting of the compounds in Table 6.

28. The use of Claim 24 wherein the compound of formula I is selected from the group consisting of the compounds in Table 8.

29. The use of Claim 25 wherein the compound of formula I is selected from the group consisting of the compounds in Table 6.

30. The use of Claim 25 wherein the compound of formula I is selected from the group consisting of the compounds in Table 8.

31. The use of Claim 26 wherein the compound of formula I is selected from the group consisting of the compounds in Table 6.

32. The use of Claim 26 wherein the compound of formula I is selected from the group consisting of the compounds in Table 8.

33. A kit comprising in a single package at least one compound of formula I as defined in Claim 1 in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising at least one additional agent for treating pain.

34. A kit comprising in a single package at least one compound of formula I as defined in Claim 1 in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising at least one additional agent for treating inflammatory pain.

35. A kit comprising in a single package at least one compound of formula I as defined in claim 1 in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising at least one additional agent for treating neuropathic pain.

36. A kit comprising in a single package at least one compound of formula I as defined in Claim 1 in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising at least one additional drug for treating diabetes.

37. A kit comprising in a single package at least one compound of formula I as defined in Claim 1 in a pharmaceutical composition for treating diabetes.

38. The use of Claim 1 wherein the absorption of cholesterol is inhibited.

39. The use of Claim 38 wherein the medicament is used with at least one additional agent for treating a disorder of lipid metabolism.

40. The use of Claim 38 wherein the medicament is used with at least one nicotinic acid receptor agonist.

41. The use of Claim 38 wherein the medicament is used with at least one inhibitor of HMG-CoA reductase.

42. The use of Claim 38 wherein the medicament is used with at least one inhibitor of CETP.

43. The use of Claim 38 wherein the medicament is used with at least one NPC1L1 antagonist.

44. The use of Claim 38 wherein the medicament is used with at least one inhibitor of HMG-CoA reductase, and with at least one NPC1L1 antagonist.

45. A kit comprising in a single package at least one compound of formula I as defined in Claim 1 in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising at least one additional drug for treating disorders of lipid metabolism.

46. A kit comprising in a single package at least one compound of formula I as defined in Claim 1 in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising at least one additional drug for inhibiting the absorption of cholesterol.