PIPERIDINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application claims the benefit of U.S. Provisional application no. 60/489,515, filed July 24, 2003, the disclosure of which is incorporated by reference herein in its entirety.

1. FIELD OF THE INVENTION

The present invention relates to Piperidine Compounds, compositions comprising an effective amount of a Piperidine Compound and methods for treating or preventing a condition such as pain comprising administering to an animal in need thereof an effective amount of a Piperidine Compound.

2. BACKGROUND OF THE INVENTION

Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limited, chronic pain persists for 3 months or longer and can lead to significant changes *in a patient's personality, lifestyle, functional ability and overall quality of life* (K.M. Foley, *Pain, in Cecil Textbook of Medicine* 100-107 (J.C. Bennett and F. Plum eds., 20th ed. 1996)).

Moreover, chronic pain can be classified as either nociceptive or neuropathic. Nociceptive pain includes tissue injury-induced pain and inflammatory pain such as that associated with arthritis. Neuropathic pain is caused by damage to the peripheral or central nervous system and is maintained by aberrant somatosensory processing. There is a large body of evidence relating activity at both Group I metabatropic glutamate receptors (mGluRs) (M.E. Fundytus, *CNS Drugs* 15:29-58 (2001)) and vanilloid receptors (V. Di Marzo *et al.*, *Current Opinion in Neurobiology* 12:372-379 (2002)) to pain processing. Inhibiting mGluR1 or mGluR5 reduces pain, as shown by in vivo treatment with antibodies selective for either mGluR1 or mGluR5, where neuropathic pain in rats was attenuated (M.E. Fundytus *et al.*, *NeuroReport* 9:731-735 (1998)). It has also been shown that antisense oligonucleotide knockdown of mGluR1 alleviates both neuropathic and inflammatory pain (M.E. Fundytus *et al.*, *British Journal of Pharmacology* 132:354-367 (2001); M.E. Fundytus *et al.*, *Pharmacology, Biochemsitry & Behavior* 73:401-410 (2002)). Small molecule antagonists for mGluR5-attenuated pain in vivo animal models are disclosed in, *e.g.*, K.

Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters* 292:115-118 (2000).

Nociceptive pain has been traditionally managed by administering non-opioid analgesics, such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusinal, and naproxen; or opioid analgesics, including morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone. *Id.* In addition to the above-listed treatments, neuropathic pain, which can be difficult to treat, has also been treated with anti-epileptics (*e.g.*, gabapentin, carbamazepine, valproic acid, topiramate, phenytoin), NMDA antagonists (*e.g.*, ketamine, dextromethorphan), topical lidocaine (for post-herpetic neuralgia), and tricyclic antidepressants (*e.g.*, fluoxetine, sertraline and amitriptyline).

UI is uncontrollable urination, generally caused by bladder-detrusor-muscle instability. UI affects people of all ages and levels of physical health, both in health care settings and in the community at large. Physiologic bladder contraction results in large part from acetylcholine-induced stimulation of post-ganglionic muscarinic-receptor sites on bladder smooth muscle. Treatments for UI include the administration of drugs having bladder-relaxant properties, which help to control bladder-detrusor-muscle overactivity. For example, anticholinergics such as propantheline bromide and glycopyrrolate, and combinations of smooth-muscle relaxants such as a combination of racemic oxybutynin and dicyclomine or an anticholinergic, have been used to treat UI (*See, e.g.*, A.J. Wein, *Urol. Clin. N. Am.* 22:557-577 (1995); Levin *et al.*, *J. Urol.* 128:396-398 (1982); Cooke *et al.*, *S. Afr. Med. J.* 63:3 (1983); R.K. Mirakhur *et al.*, *Anaesthesia* 38:1195-1204 (1983)). These drugs are not effective, however, in all patients having uninhibited bladder contractions. Administration of anticholinergic medications represent the mainstay of this type of treatment.

None of the existing commercial drug treatments for UI has achieved complete success in all classes of UI patients, nor has treatment occurred without significant adverse side effects. For example, drowsiness, dry mouth, constipation, blurred vision, headaches, tachycardia, and cardiac arrhythmia, which are related to the anticholinergic activity of traditional anti-UI drugs, can occur frequently and adversely affect patient compliance. Yet despite the prevalence of unwanted anticholinergic effects in many patients, anticholinergic drugs are currently prescribed for patients having UI. *The Merck Manual of Medical Information* 631-634 (R. Berkow ed., 1997).

Ulcers are sores occurring where the lining of the digestive tract has been eroded by stomach acids or digestive juices. The sores are typically well-defined round or oval lesions primarily occurring in the stomach and duodenum. About 1 in 10 people develop an ulcer. Ulcers develop as a result of an imbalance between acid-secretory factors, also known as "aggressive factors," such as stomach acid, pepsin, and *Helicobacter pylori* infection, and local mucosal-protective factors, such as secretion of bicarbonate, mucus, and prostaglandins.

Treatment of ulcers typically involves reducing or inhibiting the aggressive factors. For example, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate can be used to neutralize stomach acids. Antacids, however, can cause alkalosis, leading to nausea, headache, and weakness. Antacids can also interfere with the absorption of other drugs into the blood stream and cause diarrhea.

H_2 antagonists, such as cimetidine, ranitidine, famotidine, and nizatidine, are also used to treat ulcers. H_2 antagonists promote ulcer healing by reducing gastric acid and digestive-enzyme secretion elicited by histamine and other H_2 agonists in the stomach and duodenum. H_2 antagonists, however, can cause breast enlargement and impotence in men, mental changes (especially in the elderly), headache, dizziness, nausea, myalgia, diarrhea, rash, and fever.

H^+, K^+ - ATPase inhibitors such as omeprazole and lansoprazole are also used to treat ulcers. H^+, K^+ - ATPase inhibitors inhibit the production of enzymes used by the stomach to secrete acid. Side effects associated with H^+, K^+ - ATPase inhibitors include nausea, diarrhea, abdominal colic, headache, dizziness, somnolence, skin rashes, and transient elevations of plasma activities of aminotransferases.

Sucraflate is also used to treat ulcers. Sucraflate adheres to epithelial cells and is believed to form a protective coating at the base of an ulcer to promote healing. Sucraflate, however, can cause constipation, dry mouth, and interfere with the absorption of other drugs.

Antibiotics are used when *Helicobacter pylori* is the underlying cause of the ulcer. Often antibiotic therapy is coupled with the administration of bismuth compounds such as bismuth subsalicylate and colloidal bismuth citrate. The bismuth compounds are believed to enhance secretion of mucous and HCO_3^-, inhibit pepsin activity, and act as an antibacterial against *H. pylori*. Ingestion of bismuth compounds,

however, can lead to elevated plasma concentrations of Bi^{+3} and can interfere with the absorption of other drugs.

Prostaglandin analogues, such as misoprostal, inhibit secretion of acid and stimulate the secretion of mucous and bicarbonate and are also used to treat ulcers, especially ulcers in patients who require nonsteroidal anti-inflammatory drugs. Effective oral doses of prostaglandin analogues, however, can cause diarrhea and abdominal cramping. In addition, some prostaglandin analogues are abortifacients.

Carbenoxolone, a mineral corticoid, can also be used to treat ulcers. Carbenoxolone appears to alter the composition and quantity of mucous, thereby enhancing the mucosal barrier. Carbenoxolone, however, can lead to Na^+ and fluid retention, hypertension, hypokalemia, and impaired glucose tolerance.

Muscarinic cholinergic antagonists such as pirenzapine and telenzapine can also be used to reduce acid secretion and treat ulcers. Side effects of muscarinic cholinergic antagonists include dry mouth, blurred vision, and constipation. *The Merck Manual of Medical Information* 496-500 (R. Berkow ed., 1997) and *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 901-915 (J. Hardman and L. Limbird eds., 9th ed. 1996).

Inflammatory-bowel disease ("IBD") is a chronic disorder in which the bowel becomes inflamed, often causing recurring abdominal cramps and diarrhea. The two types of IBD are Crohn's disease and ulcerative colitis.

Crohn's disease, which can include regional enteritis, granulomatous ileitis, and ileocolitis, is a chronic inflammation of the intestinal wall. Crohn's disease occurs equally in both sexes and is more common in Jews of eastern-European ancestry. Most cases of Crohn's disease begin before age 30 and the majority start between the ages of 14 and 24. The disease typically affects the full thickness of the intestinal wall. Generally the disease affects the lowest portion of the small intestine (ileum) and the large intestine, but can occur in any part of the digestive tract.

Early symptoms of Crohn's disease are chronic diarrhea, crampy abdominal pain, fever, loss of appetite, and weight loss. Complications associated with Crohn's disease include the development of intestinal obstructions, abnormal connecting channels (fistulas), and abscesses. The risk of cancer of the large intestine is increased in people who have Crohn's disease. Often Crohn's disease is associated with other disorders such as gallstones, inadequate absorption of nutrients, amyloidosis, arthritis, episcleritis, aphthous stomatitis, erythema nodosum, pyoderma gangrenosum, ankylosing

spondylitis, sacroilitis, uveitis, and primary sclerosing cholangitis. There is no known cure for Crohn's disease.

Cramps and diarrhea, side effects associated with Crohn's disease, can be relieved by anticholinergic drugs, diphenoxylate, loperamide, deodorized opium tincture, or codeine. Generally, the drug is taken orally before a meal.

Broad-spectrum antibiotics are often administered to treat the symptoms of Crohn's disease. The antibiotic metronidazole is often administered when the disease affects the large intestine or causes abscesses and fistulas around the anus. Long-term use of metronidazole, however, can damage nerves, resulting in pins-and-needles sensations in the arms and legs. Sulfasalazine and chemically related drugs can suppress mild inflammation, especially in the large intestine. These drugs, however, are less effective in sudden, severe flare-ups. Corticosteroids, such as prednisone, reduce fever and diarrhea and relieve abdominal pain and tenderness. Long-term corticosteroid therapy, however, invariably results in serious side effects such as high blood-sugar levels, increased risk of infection, osteoporosis, water retention, and fragility of the skin. Drugs such as azathioprine and mercaptourine can compromise the immune system and are often effective for Crohn's disease in patients that do not respond to other drugs. These drugs, however, usually need 3 to 6 months before they produce benefits and can cause serious side effects such as allergy, pancreatitis, and low white-blood-cell count.

When Crohn's disease causes the intestine to be obstructed or when abscesses or fistulas do not heal, surgery can be necessary to remove diseased sections of the intestine. Surgery, however, does not cure the disease, and inflammation tends to recur where the intestine is rejoined. In almost half of the cases a second operation is needed. *The Merck Manual of Medical Information* 528-530 (R. Berkow ed., 1997).

Ulcerative colitis is a chronic disease in which the large intestine becomes inflamed and ulcerated, leading to episodes of bloody diarrhea, abdominal cramps, and fever. Ulcerative colitis usually begins between ages 15 and 30; however, a small group of people have their first attack between ages 50 and 70. Unlike Crohn's disease, ulcerative colitis never affects the small intestine and does not affect the full thickness of the intestine. The disease usually begins in the rectum and the sigmoid colon and eventually spreads partially or completely throughout the large intestine. The cause of ulcerative colitis is unknown.

Treatment of ulcerative colitis is directed to controlling inflammation, reducing symptoms, and replacing lost fluids and nutrients. Anticholinergic drugs and

low doses of diphenoxylate or loperamide are administered for treating mild diarrhea. For more intense diarrhea higher doses of diphenoxylate or loperamide, or deodorized opium tincture or codeine are administered. Sulfasalazine, olsalazie, prednisone, or mesalamine can be used to reduce inflammation. Azathioprine and mercaptopurine have been used to maintain remissions in ulcerative-colitis patients who would otherwise need long-term corticosteroid treatment. In severe cases of ulcerative colitis the patient is hospitalized and given corticosteroids intravenously. People with severe rectal bleeding can require transfusions and intravenous fluids. If toxic colitis develops and treatments fail, surgery to remove the large intestine can be necessary. Non-emergency surgery can be performed if cancer is diagnosed, precancerous legions are detected, or unremitting chronic disease would otherwise make the person an invalid or dependent on high doses of corticosteroids. Complete removal of the large intestine and rectum permanently cures ulcerative colitis. *The Merck Manual of Medical Information* 530-532 (R. Berkow ed., 1997) and *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (J. Hardman and L. Limbird eds., 9th ed. 1996).

Irritable-bowel syndrome ("IBS") is a disorder of motility of the entire gastrointestinal tract, causing abdominal pain, constipation, and/or diarrhea. IBS affects three-times more women than men. In IBS stimuli such as stress, diet, drugs, hormones, or irritants can cause the gastrointestinal tract to contract abnormally. During an episode of IBS, contractions of the gastrointestinal tract become stronger and more frequent, resulting in the rapid transit of food and feces through the small intestine, often leading to diarrhea. Cramps result from the strong contractions of the large intestine and increased sensitivity of pain receptors in the large intestine.

There are two major types of IBS. The first type, spastic-colon type, is commonly triggered by eating, and usually produces periodic constipation and diarrhea with pain. Mucous often appears in the stool. The pain can come in bouts of continuous dull aching pain or cramps, usually in the lower abdomen. The person suffering from spastic-colon type IBS can also experience bloating, gas, nausea, headache, fatigue, depression, anxiety, and difficulty concentrating. The second type of IBS usually produces painless diarrhea or constipation. The diarrhea can begin suddenly and with extreme urgency. Often the diarrhea occurs soon after a meal and can sometimes occur immediately upon awakening.

Treatment of IBS typically involves modification of an IBS-patient's diet. Often it is recommended that an IBS patient avoid beans, cabbage, sorbitol, and fructose.

A low-fat, high-fiber diet can also help some IBS patients. Regular physical activity can also help keep the gastrointestinal tract functioning properly. Drugs such as propantheline that slow the function of the gastrointestinal tract are generally not effective for treating IBS. Antidiarrheal drugs, such as diphenoxylate and loperamide, help with diarrhea. *The Merck Manual of Medical Information* 525-526 (R. Berkow ed., 1997).

Certain pharmaceutical agents have been administered for treating addiction. U.S. Patent No. 5,556,838 to Mayer *et al.* discloses the use of nontoxic NMDA-blocking agents co-administered with an addictive substance to prevent the development of tolerance or withdrawal symptoms. U.S. Patent No. 5,574,052 to Rose *et al.* discloses co-administration of an addictive substance with an antagonist to partially block the pharmacological effects of the addictive substance. U.S. Patent No. 5,075,341 to Mendelson *et al.* discloses the use of a mixed opiate agonist/antagonist to treat cocaine and opiate addiction. U.S. Patent No. 5,232,934 to Downs discloses administration of 3-phenoxypyridine to treat addiction. U.S. Patents No. 5,039,680 and 5,198,459 to Imperato *et al.* disclose using a serotonin antagonist to treat chemical addiction. U.S. Patent No. 5,556,837 to Nestler et. al. discloses infusing BDNF or NT-4 growth factors to inhibit or reverse neurological adaptive changes that correlate with behavioral changes in an addicted individual. U.S. Patent. No. 5,762,925 to Sagan discloses implanting encapsulated adrenal medullary cells into an animal's central nervous system to inhibit the development of opioid intolerance. U.S. Patent No. 6,204,284 to Beer *et al.* discloses racemic (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane for use in the prevention or relief of a withdrawal syndrome resulting from addiction to drugs and for the treatment of chemical dependencies.

Without treatment, Parkinson's disease progresses to a rigid akinetic state in which patients are incapable of caring for themselves. Death frequently results from complications of immobility, including aspiration pneumonia or pulmonary embolism. Drugs commonly used for the treatment of Parkinson's disease include carbidopa/levodopa, pergolide, bromocriptine, selegiline, amantadine, and trihexyphenidyl hydrochloride. There remains, however, a need for drugs useful for the treatment of Parkinson's disease and having an improved therapeutic profile.

Currently, benzodiazepines are the most commonly used anti-anxiety agents for generalized anxiety disorder. Benzodiazepines, however, carry the risk of producing impairment of cognition and skilled motor functions, particularly in the

elderly, which can result in confusion, delerium, and falls with fractures. Sedatives are also commonly prescribed for treating anxiety. The azapirones, such as buspirone, are also used to treat moderate anxiety. The azapirones, however, are less useful for treating severe anxiety accompanied with panic attacks.

Examples of drugs for treating a seizure and epilepsy include carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, γ-vinyl GABA, acetazolamide, and felbamate. Anti-seizure drugs, however, can have side effects such as drowsiness; hyperactivity; hallucinations; inability to concentrate; central and peripheral nervous system toxicity, such as nystagmus, ataxia, diplopia, and vertigo; gingival hyperplasia; gastrointestinal disturbances such as nausea, vomiting, epigastric pain, and anorexia; endocrine effects such as inhibition of antidiuretic hormone, hyperglycemia, glycosuria, osteomalacia; and hypersensitivity such as scarlatiniform rash, morbilliform rash, Stevens-Johnson syndrome, systemic lupus erythematosus, and hepatic necrosis; and hematological reactions such as red-cell aplasia, agranulocytosis, thrombocytopenia, aplastic anemia, and megaloblastic anemia. *The Merck Manual of Medical Information* 345-350 (R. Berkow ed., 1997).

Symptoms of strokes vary depending on what part of the brain is affected. Symptoms include loss or abnormal sensations in an arm or leg or one side of the body, weakness or paralysis of an arm or leg or one side of the body, partial loss of vison or hearing, double vision, dizziness, slurred speech, difficulty in thinking of the appropriate word or saying it, inability to recognize parts of the body, unusual movements, loss of bladder control, imbalance, and falling, and fainting. The symptoms can be permanent and can be associated with coma or stupor. Examples of drugs for treating strokes include anticoagulants such as heparin, drugs that break up clots such as streptokinase or tissue plasminogen activator, and drugs that reduce swelling such as mannitol or corticosteroids. *The Merck Manual of Medical Information* 352-355 (R. Berkow ed., 1997).

Pruritus is an unpleasant sensation that prompts scratching. Conventionally, pruritus is treated by phototherapy with ultraviolet B or PUVA or with therapeutic agents such as naltrexone, nalmefene, danazol, tricyclics, and antidepressants.

Selective antagonists of the metabotropic glutamate receptor 5 ("mGluR5") have been shown to exert analgesic activity in *in vivo* animal models (K.

Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters*, 292(2):115-118 (2000)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anxiolytic and anti-depressant activity in *in vivo* animal models (E. Tatarczynska *et al.*, *Br. J. Pharmacol.* 132(7):1423-1430 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anti-Parkinson activity *in vivo* (K. J. Ossowska *et al.*, *Neuropharmacology* 41(4):413-20 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anti-dependence activity *in vivo* (C. Chiamulera *et al.*, *Nature Neuroscience* 4(9):873-74 (2001)).

International publication no. WO 01/027107 describes a class of heterocyclic compounds that are sodium/proton exchange inhibitors.

International publication no. WO 99/37304 describes substituted oxoazaheterocycly compounds useful for inhibiting factor Xa.

U.S. Patent No. 6,248,756 to Anthony *et al.* and international publication no. WO 97/38665 describe a class of piperidine-containing compounds that inhibit farnesyl-protein transferase (Ftase).

International publication no. WO 98/31669 describes a class of aromatic amines derived from cyclic amines useful as antidepressant drugs.

International publication no. WO 97/28140 describes a class of piperidines derived from 1-(piperazin-1-yl)aryl(oxy/amino)carbonyl-4-aryl-piperidine that are useful as 5-HT_{1Db} receptor antagonists.

International publication no. WO 97/38665 describes a class of piperidine containing compounds that are useful as inhibitors of farnesyl-protein transferase.

U.S. Patent No. 4,797,419 to Moos *et al.* describes a class of urea compounds for stimulating the release of acetylcholine and useful for treating symptoms of senile cognitive decline, characterized by decreased cerebral acetylcholine production or release.

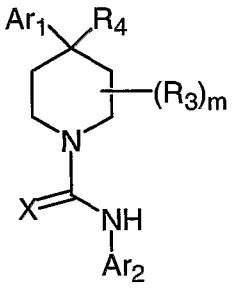
U.S. Patent No. 5,891,889 describes a class of substituted piperidine compounds that are useful as inhibitors of farnesyl-protein transferase, and the farnesylation of the oncogene protein Ras.

There remains, however, a clear need in the art for new drugs useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application.

3. SUMMARY OF THE INVENTION

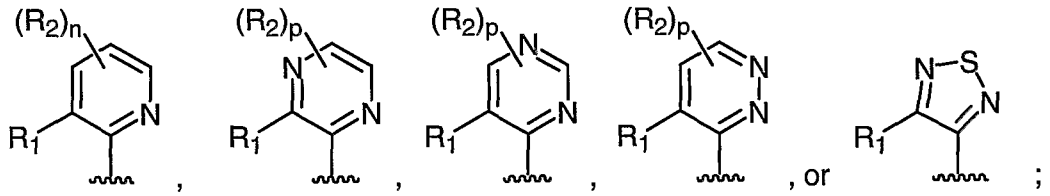
The present invention encompasses compounds of formula (I):



(I)

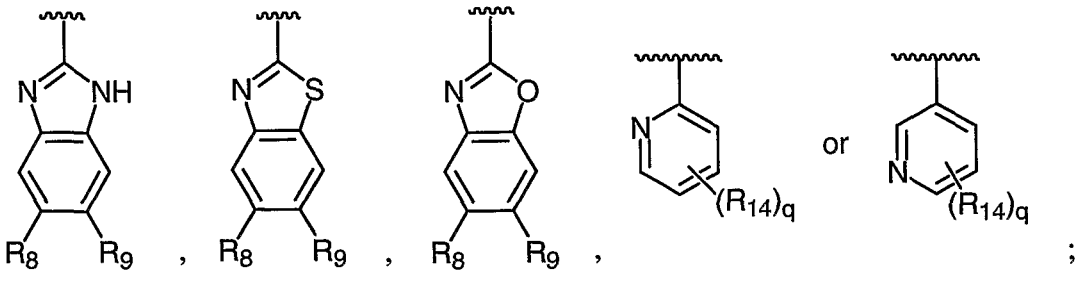
and pharmaceutically acceptable salts thereof, where

Ar_1 is



;

Ar_2 is



;

X is O, S, N-CN, N-OH, or N-OR_{10};

R_1 is -H, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -OH, -CN, NO_2, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

R_4 is -OH, $-OCF_3$, -halo, $-(C_1-C_6)$alkyl, $-CH_2OH$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-CH_2F$, $-CH(halo)_2$, $-CF_3$, $-OR_{10}$, $-SR_{13}$, -COOH, $-COOR_{10}$, $-C(O)R_{10}$, -C(O)H, $-OC(O)R_{10}$, $-OC(O)NHR_{10}$, $-NHC(O)R_{13}$, $-CON(R_{13})_2$, $-SO_2R_{10}$, or NO_2;

each R_5 is independently -CN, -OH, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, or $-OC(O)OR_7$;

each R_6 is independently $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

each R_7 is independently -H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, or $CH_2(halo)$;

R_8 and R_9 are each independently -H, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -$(C_3$-$C_8)$cycloalkyl, -$(C_5$-$C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -$CH_2C(halo)_3$, -$C(halo)_3$, -$CH(halo)_2$, -$CH_2(halo)$, -CN, -OH, -halo, -N_3, -NO_2, -$CH{=}NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

R_{10} is -$(C_1$-$C_4)$alkyl;

each R_{13} is independently:

(a) -H, or -$(C_1$-$C_4)$alkyl; or

(b) -phenyl or -(3- to 5-membered)heteroaryl each of which is unsubstituted or substituted with one or more R_6 groups;

each R_{14} is independently -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -$(C_3$-$C_8)$cycloalkyl, -$(C_5$-$C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -$CH_2C(halo)_3$, -$C(halo)_3$, -$CH(halo)_2$, -$CH_2(halo)$, -CN, -OH, -halo, -N_3, -NO_2, -$CH{=}NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

each halo is independently -F, -Cl, -Br, or -I;

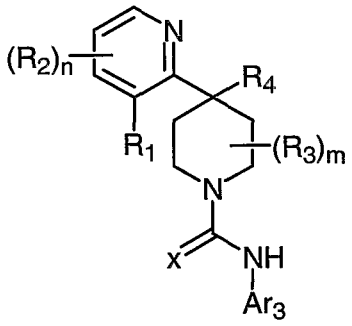
n is an integer ranging from 0 to 3;

p is an integer ranging from 0 to 2;

q is an integer ranging from 0 to 4; and

m is 0 or 1.

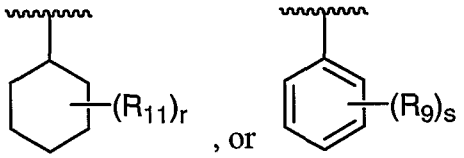
The invention further encompasses compounds of formula (II):



(II)

and pharmaceutically acceptable salts thereof, where

Ar_3 is



;

X is O, S, N-CN, N-OH, or N-OR_{10};

R_1 is -halo, -CH_3, -NO_2, -CN, -OH, -OCH_3, -NH_2, C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each R_2 is independently:

(a) -halo, -OH, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, -NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

R_4 is -OH, -OCF_3, -halo, -(C_1-C_6)alkyl, -CH_2OH, -CH_2Cl, -CH_2Br, -CH_2I, -CH_2F, -CH(halo)$_2$, -CF_3, -OR_{10}, -SR_{13}, -COOH, -$COOR_{10}$, -C(O)R_{10}, -C(O)H, -OC(O)R_{10}, -OC(O)NHR_{10}, -NHC(O)R_{13}, -CON(R_{13})$_2$, -SO_2R_{10}, or NO_2;

each R_5 is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, or -OC(O)OR_7;

each R_6 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$;

each R_7 is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or CH_2(halo);

each R_9 is -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -$CH_2C(halo)_3$, -$C(halo)_3$, -$CH(halo)_2$, -$CH_2(halo)$, -CN, -OH, -halo, -N_3, -NO_2, -$CH{=}NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

R_{10} is -(C_1-C_4)alkyl;

each R_{11} is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -$CH{=}NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, or -$OC(O)OR_7$;

each R_{13} is independently:

(a) -H or -(C_1-C_4)alkyl; or

(b) -phenyl or -(3- to 5-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each halo is independently -F, -Cl, -Br, or -I;

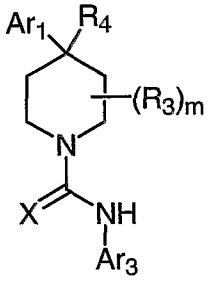
n is an integer ranging from 0 to 3;

r is an integer ranging from 0 to 6;

s is an integer ranging from 0 to 5; and

m is 0 or 1.

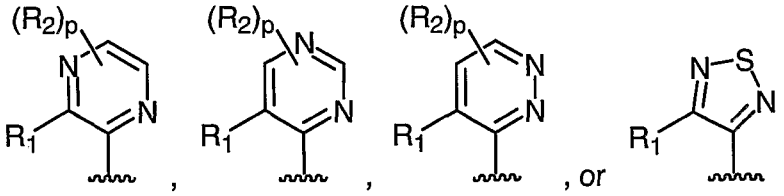
The invention further encompasses compounds of formula (III):



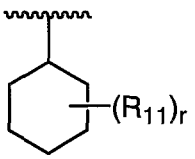
(III)

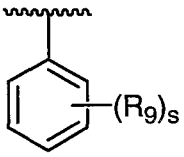
and pharmaceutically acceptable salts thereof, where

Ar_1 is



Ar_3 is



, or


;

X is O, S, N -CN, N-OH, or N-OR_{10};

R_1 is -H, -halo, -CH_3, -NO_2, -CN, -OH, -OCH_3, -NH_2, C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each R_2 is independently:

(a) -halo, -OH, -CN, NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, -NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

R_4 is -OH, -OCF_3, -halo, -(C_1-C_6)alkyl, -CH_2OH, -CH_2Cl, -CH_2Br, -CH_2I, -CH_2F, -CH(halo)$_2$, -CF_3, -OR_{10}, -SR_{13}, -COOH, -$COOR_{10}$, -C(O)R_{10}, -C(O)H, -OC(O)R_{10}, -OC(O)NHR_{10}, -NHC(O)R_{13}, -CON(R_{13})$_2$, -SO_2R_{10}, or NO_2;

each R_5 is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, or -OC(O)OR_7;

each R_6 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo),

-CN, -OH, -halo, -N_3, -NO_2, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$;

each R_7 is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or CH_2(halo);

each R_9 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -CH_2C(halo)$_3$, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$;

R_{10} is -(C_1-C_4)alkyl;

each R_{11} is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, or -OC(O)OR_7;

each R_{13} is independently:

(a) -H or -(C_1-C_4)alkyl; or

(b) -phenyl or -(3- to 5-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each halo is independently -F, -Cl, -Br, or -I;

p is an integer ranging from 0 to 2;

r is an integer ranging from 0-6;

s is an integer ranging from 0-5; and

m is 0 or 1.

A compound of formula (I), (II) or (III) or a pharmaceutically acceptable salt thereof (a "Piperidine Compound"), is useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression (each being a "Condition") in an animal.

The invention also relates to compositions comprising an effective amount of a Piperidine Compound and a pharmaceutically acceptable carrier or excipient. The compositions are useful for treating or preventing a Condition in an animal.

The invention further relates to methods for treating a Condition comprising administering to an animal in need thereof an effective amount of a Piperidine Compound.

The invention further relates to methods for preventing a Condition comprising administering to an animal in need thereof an effective amount of a Piperidine Compound.

The invention still further relates to methods for inhibiting Vanilloid Receptor 1 ("VR1") function in a cell, comprising contacting a cell capable of expressing VR1 with an effective amount of a Piperidine Compound.

The invention still further relates to methods for inhibiting mGluR5 function in a cell, comprising contacting a cell capable of expressing mGluR5 with an effective amount of a Piperidine Compound.

The invention still further relates to methods for inhibiting metabotropic glutamate receptor 1 ("mGluR1") function in a cell, comprising contacting a cell capable of expressing mGluR1 with an effective amount of a Piperidine Compound.

The invention still further relates to a method for preparing a composition comprising the step of admixing a Piperidine Compound and a pharmaceutically acceptable carrier or excipient.

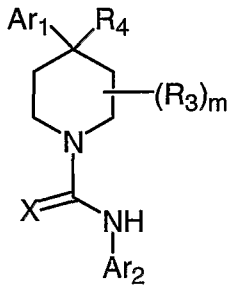
The invention still further relates to a kit comprising a container containing an effective amount of a Piperidine Compound.

The present invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 PIPERIDINE COMPOUNDS OF FORMULA (I)

As stated above, the present invention encompasses compounds of Formula (I)



(I)

and pharmaceutically acceptable salts thereof, where Ar_1, Ar_2, R_3, R_4, X, and m are defined above for the Piperidine Compounds of formula (I).

In one embodiment, Ar_1 is a pyridyl group.

In another embodiment, Ar_1 is a pyrimidyl group

In another embodiment, Ar_1 is a pyrazinyl group.

In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a thiazanyl group.

In another embodiment, X is O.

In another embodiment, X is S.

In another embodiment, X is N-CN.

In another embodiment, X is N-OH.

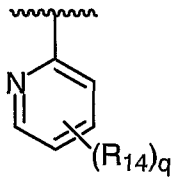
In another embodiment, X is N-OR_{10}.

In another embodiment, Ar_2 is a benzoimidazolyl group.

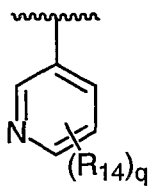
In another embodiment, Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, n or p is 0.

In another embodiment, n or p is 1.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, R_1 is -H.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -CN.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, n or p is 1 and R_2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, n or p is 1 and R_2 is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, n or p is 1 and R_2 is -phenyl, -naphthyl, $-(C_{14})$aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

In another embodiment, m is 1 and R_3 is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, $-(C_{14})$aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is $-CH_3$.

In another embodiment, R_4 is -OH.

In another embodiment, R_4 is $-OCF_3$

In another embodiment, R_4 is -halo.

In another embodiment, R_4 is $-(C_1-C_6)$alkyl.

In another embodiment, R_4 is $-CH_3$.

In another embodiment, R_4 is $-CH_2OH$.

In another embodiment, R_4 is $-CH_2Cl$.

In another embodiment, R_4 is $-CH_2Br$.

In another embodiment, R_4 is $-CH_2I$.

In another embodiment, R_4 is $-CH_2F$.

In another embodiment, R_4 is $-CH(halo)_2$.

In another embodiment, R_4 is $-CF_3$.

In another embodiment, R_4 is $-NO_2$.

In another embodiment, R_4 is $-OR_{10}$.

In another embodiment, R_4 is $-SR_{13}$.

In another embodiment, R_4 is $-C(O)R_{10}$.

In another embodiment, R_4 is -COOH.

In another embodiment, R_4 is -C(O)H.

In another embodiment, R_4 is $-COOR_{10}$.

In another embodiment, R_4 is $-OC(O)R_{10}$.

In another embodiment, R_4 is $-SO_2R_{10}$.

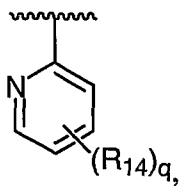
In another embodiment, R_4 is $-OC(O)NHR_{10}$.

In another embodiment, R_4 is $-NHC(O)R_{13}$.

In another embodiment, R_4 is $-CON(R_{13})_2$.

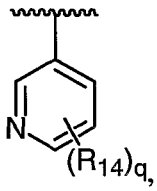
In another embodiment, Ar_2 is a benzothiazolyl, benzoimidazolyl, or benzooxazolyl group; and at least one of R_8 and R_9 is -H.

In another embodiment, Ar_2 is



and q is 1.

In another embodiment, Ar_2 is



and q is 1.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -F, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -I, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -F, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -I, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is a benzooxazolyl group.

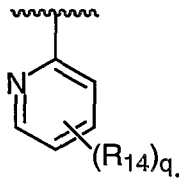
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -F, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is a benzooxazolyl group.

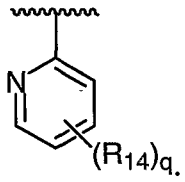
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -I, and Ar_2 is a benzooxazolyl group.

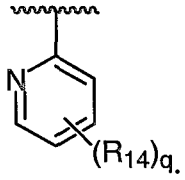
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is



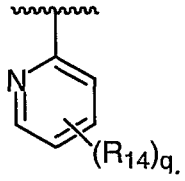
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -F, and Ar_2 is



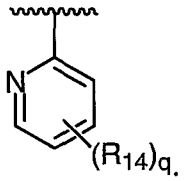
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is



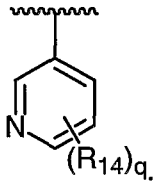
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is



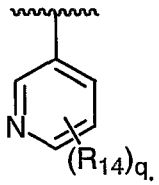
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -I, and Ar_2 is



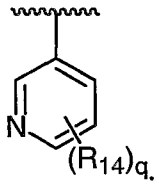
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is



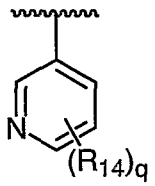
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -F, and Ar_2 is



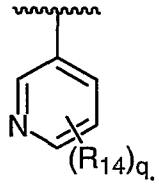
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is



In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is



In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -I, and Ar_2 is

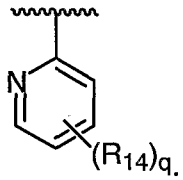


In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is a benzothiazolyl group.

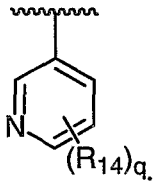
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is



In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is

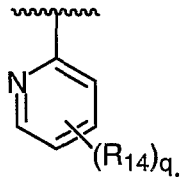


In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is a benzothiazolyl group.

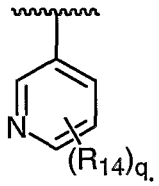
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is



In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is

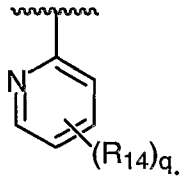


In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is a benzothiazolyl group.

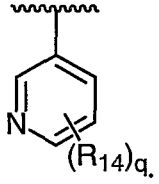
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-OR_{10}$ and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is



In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is

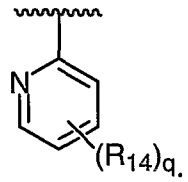


In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is a benzothiazolyl group.

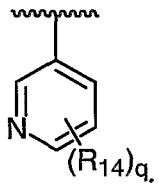
In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is a benzooxazozolyl group.

In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is



In another embodiment, Ar_1 is a pyridyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is



In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -F, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -I, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -F, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -I, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is a benzooxazolyl group.

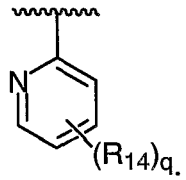
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -F, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is a benzooxazolyl group.

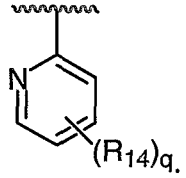
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -I, and Ar_2 is a benzooxazolyl group.

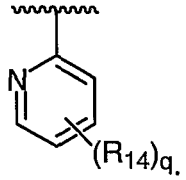
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is



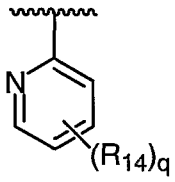
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -F, and Ar_2 is



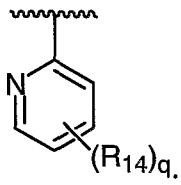
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is



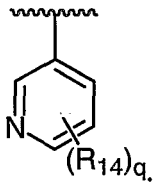
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is



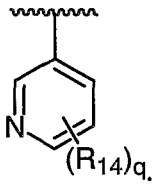
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -I, and Ar_2 is



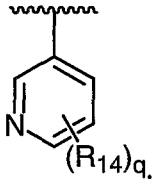
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -halo, and Ar_2 is



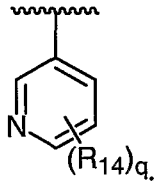
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -F, and Ar_2 is



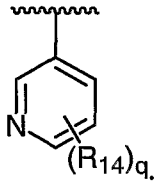
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Cl, and Ar_2 is



In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -Br, and Ar_2 is



In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -I, and Ar_2 is

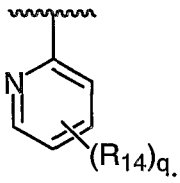


In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is a benzothiazolyl group.

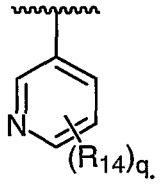
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is



In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is -OH, and Ar_2 is



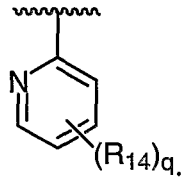
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is a benzoimidazolyl group.

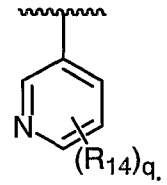
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is a cyclohexyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is



In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_2 is

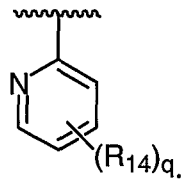


In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is a benzothiazolyl group.

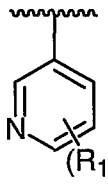
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is



In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_2 is

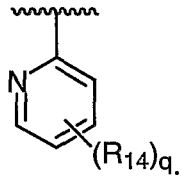


In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is a benzothiazolyl group.

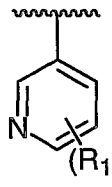
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is

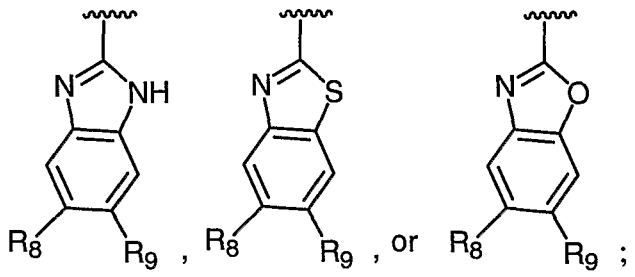


In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_2 is



The invention also relates compounds of formula (I), and pharmaceutically acceptable salts thereof, where:

Ar_2 is



each R_3 is independently:

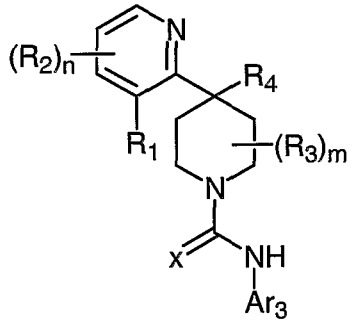
(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, each of which is unsubstituted or substituted with one or more R_5 groups; and

at least one of R_8 or R_9 is other than -H.

4.2 PIPERIDINE COMPOUNDS OF FORMULA (II)

This invention also relates to compounds of formula (II):



(II)

and pharmaceutically acceptable salts thereof, where R_1, R_2, Ar_3, R_3, R_4, X, n and m are defined above for the Piperidine Compounds of formula (II).

In one embodiment, X is O.

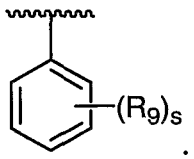
In another embodiment, X is S.

In another embodiment, X is N-CN.

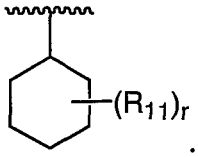
In another embodiment, X is N-OH.

In another embodiment, X is $N-OR_{10}$.

In another embodiment, Ar_3 is



In another embodiment, Ar_3 is



It is to be understood that when two R_{11} groups are present on the same carbon atom, the two R_{11} groups on the same carbon atom are not both -CN, -OH, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-COR_7$, $-OC(O)R_7$, or $-OC(O)OR_7$.

In another embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is-CH_3.

In another embodiment, R_1 is-NO_2.

In another embodiment, R_1 is-CN.

In another embodiment, R_1 is-OH.

In another embodiment, R_1 is-OCH_3.

In another embodiment, R_1 is-NH_2.

In another embodiment, R_1 is-$C(halo)_3$.

In another embodiment, R_1 is-$CH(halo)_2$.

In another embodiment, R_1 is-$CH_2(halo)$.

In another embodiment, n is 1 and R_2 is -halo, -OH, or $-NH_2$.

In another embodiment, n is 1 and R_2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, n is 1 and R_2 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

In another embodiment, m is 1 and R_3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is -CH_3.

In another embodiment, R_4 is -OH.

In another embodiment, R_4 is $-OCF_3$

In another embodiment, R_4 is -halo.

In another embodiment, R_4 is $-(C_1\text{-}C_6)$alkyl.

In another embodiment, R_4 is $-CH_3$.

In another embodiment, R_4 is $-CH_2OH$.

In another embodiment, R_4 is $-CH_2Cl$.

In another embodiment, R_4 is $-CH_2Br$.

In another embodiment, R_4 is $-CH_2I$.

In another embodiment, R_4 is $-CH_2F$.

In another embodiment, R_4 is $-CH(halo)_2$.

In another embodiment, R_4 is $-CF_3$.

In another embodiment, R_4 is $-NO_2$.

In another embodiment, R_4 is $-OR_{10}$.

In another embodiment, R_4 is $-SR_{13}$.

In another embodiment, R_4 is $-C(O)R_{10}$.

In another embodiment, R_4 is -COOH.

In another embodiment, R_4 is -C(O)H.

In another embodiment, R_4 is $-COOR_{10}$.

In another embodiment, R_4 is $-C(O)OR_{10}$.

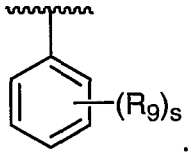
In another embodiment, R_4 is $-SO_2R_{10}$.

In another embodiment, R_4 is $-OC(O)NHR_{10}$.

In another embodiment, R_4 is $-NHC(O)R_{13}$.

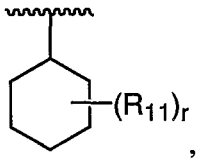
In another embodiment, R_4 is $-CON(R_{13})_2$.

In another embodiment, Ar_3 is



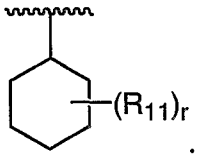
and s is 1.

In another embodiment, Ar_3 is

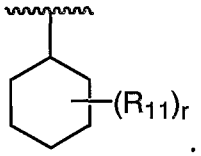


and r is 1.

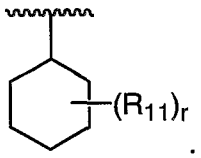
In another embodiment, X is O, m is 0, R_4 is -halo, and Ar_3 is



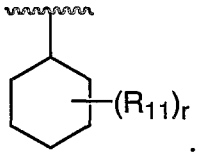
In another embodiment, X is O, m is 0, R_4 is -F, and Ar_3 is



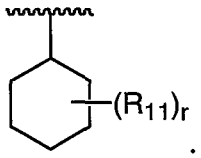
In another embodiment, X is O, m is 0, R_4 is -Cl, and Ar_3 is



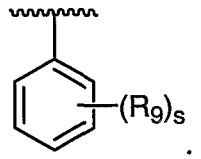
In another embodiment, X is O, m is 0, R_4 is -Br, and Ar_3 is



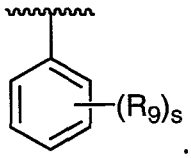
In another embodiment, X is O, m is 0, R_4 is -I, and Ar_3 is



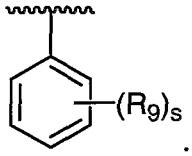
In another embodiment, X is O, m is 0, R_4 is -halo, and Ar_3 is



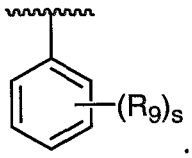
In another embodiment, X is O, m is 0, R_4 is -F, and Ar_3 is



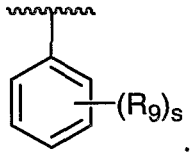
In another embodiment, X is O, m is 0, R_4 is -Cl, and Ar_3 is



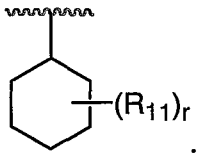
In another embodiment, X is O, m is 0, R_4 is -Br, and Ar_3 is



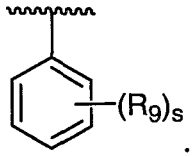
In another embodiment, X is O, m is 0, R_4 is -I, and Ar_3 is



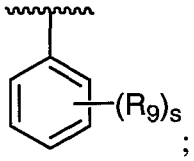
In another embodiment, X is O, m is 0, R_4 is -OH, and Ar_3 is



In another embodiment, X is O, m is 0, R_4 is -OH, and Ar_3 is



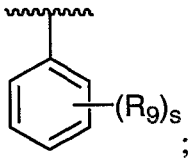
In another embodiment, X is O, m is 0, R_4 is -OH, and Ar_3 is



;

s is 1; and R_9 is -(C_1-C_6)alkyl.

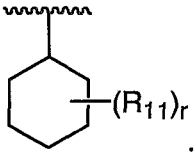
In another embodiment, X is O, m is 0, R_4 is -OH, and Ar_3 is



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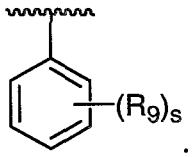
s is 1; and R_9 is -CH_3.

In another embodiment, X is O, m is 0, R_4 is -CH_3, and Ar_3 is



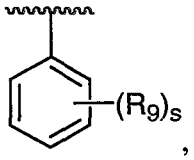
.

In another embodiment, X is O, m is 0, R_4 is -CH_3, and Ar_3 is



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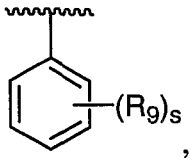
In another embodiment, X is O, m is 0, R_4 is -CH_3, and Ar_3 is



,

s is 1, and R_9 is -(C_1-C_6)alkyl.

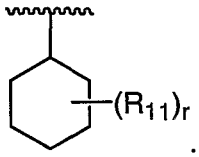
In another embodiment, X is O, m is 0, R_4 is -CH_3, and Ar_3 is



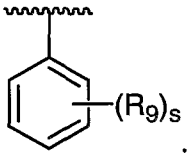
,

s is 1, and R_9 is -CH_3.

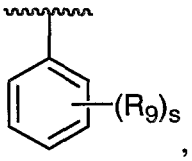
In another embodiment, X is O, m is 0, R_4 is -OR_{10}, and Ar_3 is



In another embodiment, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_3 is

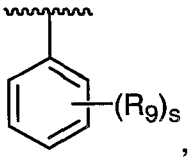


In another embodiment, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_3 is



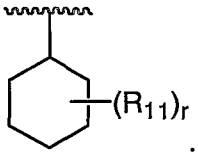
s is 1, and R_9 is $-(C_1-C_6)$alkyl.

In another embodiment, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_3 is

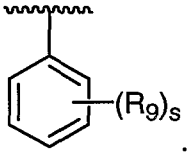


s is 1, and R_9 is $-CH_3$.

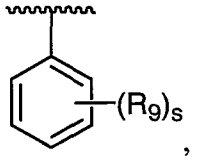
In another embodiment, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_3 is



In another embodiment, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_3 is



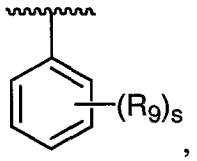
In another embodiment, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_3 is



,

s is 1, and R_9 is -(C_1-C_6)alkyl.

In another embodiment, X is O, m is 0, R_4 is -C(O)R_{10}, and Ar_3 is

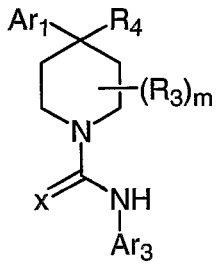


,

s is 1, and R_9 is -CH_3.

4.3 PIPERIDINE COMPOUNDS OF FORMULA (III)

The invention also relates to compounds of formula (III):



(III)

and pharmaceutically acceptable salts thereof, where Ar_1, Ar_3, R_3, R_4, X and m are defined above for the Piperidine Compounds of formula (III).

In one embodiment, X is O.

In another embodiment, X is S.

In another embodiment, X is N-CN.

In another embodiment, X is N-OH.

In another embodiment, X is N-OR_{10}.

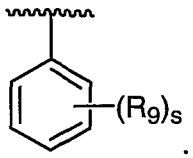
In another embodiment, Ar_1 is a pyrimidyl group.

In another embodiment, Ar_1 is a pyrazinyl group.

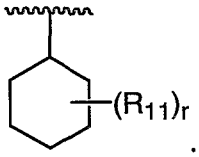
In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a thiazanyl group.

In another embodiment, Ar_3 is



In another embodiment, Ar_3



It is to be understood that when two R_{11} groups are present on the same carbon atom, the two R_{11} groups on the same carbon atom are not both -CN, -OH, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-COR_7$, $-OC(O)R_7$, or $-OC(O)OR_7$.

In another embodiment, p is 0.

In another embodiment, p is 1.

In another embodiment, R_1 is -H.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is-CH_3.

In another embodiment, R_1 is-NO_2.

In another embodiment, R_1 is-CN.

In another embodiment, R_1 is-OH.

In another embodiment, R_1 is-OCH_3.

In another embodiment, R_1 is-NH_2.

In another embodiment, R_1 is-$C(halo)_3$.

In another embodiment, R_1 is-$CH(halo)_2$.

In another embodiment, R_1 is-$CH_2(halo)$.

In another embodiment, p is 1 and R_2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, p is 1 and R_2 is -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_8$-$C_{14})$tricycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -$(C_8$-$C_{14})$bicycloalkenyl, -$(C_8$-$C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, p is 1 and R_2 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, -NO_2, or -NH_2;

In another embodiment, m is 1 and R_3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is -CH_3.

In another embodiment, R_4 is -OH.

In another embodiment, R_4 is -OCF_3

In another embodiment, R_4 is -halo.

In another embodiment, R_4 is -(C_1-C_6)alkyl.

In another embodiment, R_4 is - CH_3.

In another embodiment, R_4 is -CH_2OH.

In another embodiment, R_4 is -CH_2Cl.

In another embodiment, R_4 is -CH_2Br.

In another embodiment, R_4 is -CH_2I.

In another embodiment, R_4 is -CH_2F.

In another embodiment, R_4 is -CH(halo)$_2$.

In another embodiment, R_4 is -CF_3.

In another embodiment, R_4 is -NO_2.

In another embodiment, R_4 is -OR_{10}.

In another embodiment, R_4 is -SR_{13}.

In another embodiment, R_4 is -C(O)R_{10}.

In another embodiment, R_4 is -COOH.

In another embodiment, R_4 is -C(O)H.

In another embodiment, R_4 is -$COOR_{10}$.

In another embodiment, R_4 is -$OC(O)R_{10}$.

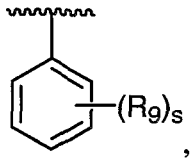
In another embodiment, R_4 is -SO_2R_{10}.

In another embodiment, R_4 is -OC(O)NHR$_{10}$.

In another embodiment, R_4 is -NHC(O)R$_{13}$.

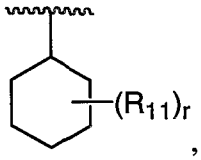
In another embodiment, R_4 is - CON(R$_{13}$)$_2$.

In another embodiment, Ar_3 is



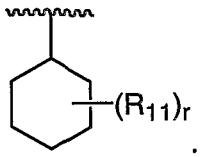
and s is 1.

In another embodiment, Ar_3 is

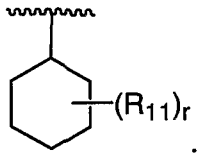


and r is 1.

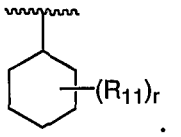
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -halo, and Ar_3 is



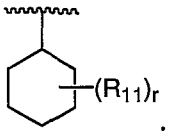
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -F, and Ar_3 is



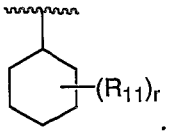
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -Cl, and Ar_3 is



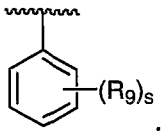
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -Br, and Ar_3 is



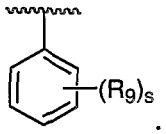
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -I, and Ar_3 is



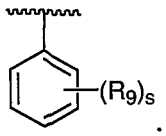
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -halo, and Ar_3 is



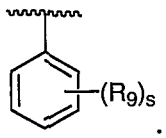
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -F, and Ar_3 is



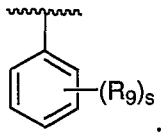
In another embodiment, X is O, m is 0, R_4 is -Cl, and Ar_3 is



In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -Br, and Ar_3 is

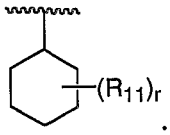


In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -I, and Ar_3 is



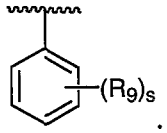
.

In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -OH, and Ar_3 is



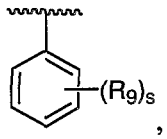
.

In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -OH, and Ar_3 is



.

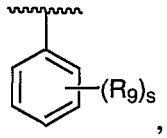
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -OH, and Ar_3 is



,

where s is 1, and R_9 is -(C_1-C_6)alkyl.

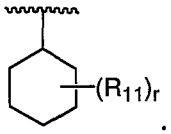
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -OH, and Ar_3 is



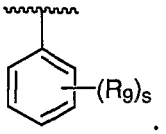
,

where s is 1, and R_9 is -CH_3.

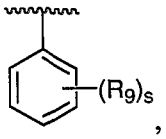
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is -CH_3, and Ar_3 is



In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_3 is

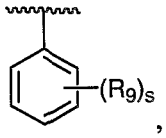


In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_3 is



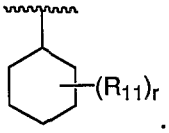
and s is 1, and R_9 is $-(C_1-C_6)$alkyl.

In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-CH_3$, and Ar_3 is

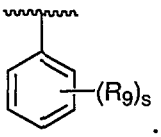


where s is 1, and R_9 is $-CH_3$.

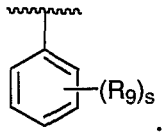
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_3 is



In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_3 is

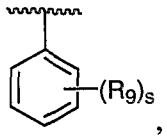


In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_3 is



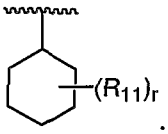
s is 1, and R_9 is $-(C_1-C_6)$alkyl.

In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-OR_{10}$, and Ar_3 is

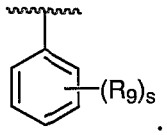


s is 1, and R_9 is $-CH_3$.

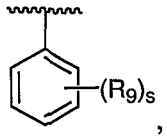
In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_3 is



In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_3 is

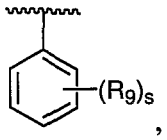


In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_3 is



s is 1, and R_9 is $-(C_1-C_6)$alkyl.

In another embodiment, Ar_1 is a pyradizinyl group, X is O, m is 0, R_4 is $-C(O)R_{10}$, and Ar_3 is



s is 1, and R_9 is $-CH_3$.

4.4 PIPERIDINE COMPOUNDS OF FORMULAS (I) - (III)

In the Piperidine Compounds that have an R_3 group, the R_3 group can be attached to a carbon atom adjacent to the carbon atom attached to the R_4 group, or the R_3 group can be attached to a carbon atom adjacent to the nitrogen atom attached to the $-C(X)NH-Ar_2$ or $-C(X)NH-Ar_3$ group. In one embodiment, the R_3 group is attached to a carbon atom adjacent to the carbon atom attached to the R_4 group. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached $-C(X)NH-Ar_2$ or $-C(X)NH-Ar_3$ group.

In one embodiment, where the Piperidine Compound has an R_3 group, the carbon atom to which the R_3 group is attached has the (R) configuration. In another embodiment, where the Piperidine Compound has an R_3 group, the carbon atom to which the R_3 group is attached has the (S) configuration.

In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon atom attached to the R_4 group, and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is $-(C_1-C_4)$alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is $-CH_3$. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is $-CF_3$. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is $-CH_2CH_3$.

In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -

C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is -CH_3. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is -CF_3. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is -CH_2CH_3.

In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon atom attached to the R_4 group, and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -CH_3. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -CF_3. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the carbon attached to the R_4 group, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -CH_2CH_3.

In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Piperidine Compound has an R_3

group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 group or -C(X)NH-Ar_3, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -CH_3. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -CF_3. In another embodiment, the Piperidine Compound has an R_3 group, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -CH_2CH_3.

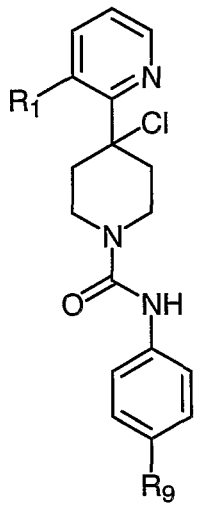
In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, and the R_3 group is a -CH_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, and the R_3 group is a -CF_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, and the R_3 group is a -CH_2CH_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (R) configuration, and the R_3 group is a -CH_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (R) configuration, and the R_3 group is a -CF_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(X)NH-Ar_2 or -C(X)NH-Ar_3 group, the carbon to which the R_3 group is attached is in the (R) configuration, and the R_3 group is a -CH_2CH_3.

In another embodiment, m is 1 and R_3 is *cis* to R_4.

In another embodiment, m is 1 and R_3 is *trans* to R_4.

Illustrative Piperidine Compounds are listed below in Tables 1-18:

Table 1



(IIa)

and pharmaceutically acceptable salts thereof, where:

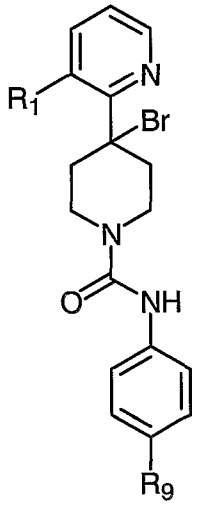
Compound	R_1	R_9
AAA	-Cl	-H
AAB	-Cl	-*tert*-butyl
AAC	-Cl	-*iso*-butyl
AAD	-Cl	-*sec*-butyl
AAE	-Cl	-cyclohexyl
AAF	-Cl	-*tert*-butoxy
AAG	-Cl	-*iso*-propoxy
AAH	-Cl	$-CF_3$
AAI	-Cl	$-CH_2CF_3$
AAJ	-Cl	$-OCF_3$
AAK	-Cl	-Cl
AAL	-Cl	-Br
AAM	-Cl	-I
AAN	-Cl	-n-butyl
AAO	-Cl	-n-propyl
AAP	-F	-H
AAQ	-F	-*tert*-butyl
AAR	-F	-*iso*-butyl
AAS	-F	-*sec*-butyl
AAT	-F	-cyclohexyl
AAU	-F	-*tert*-butoxy
AAV	-F	-*iso*-propoxy
AAW	-F	$-CF_3$
AAX	-F	$-CH_2CF_3$
AAY	-F	$-OCF_3$
AAZ	-F	-Cl

ABA	-F	-Br
ABB	-F	-I
ABC	-F	-n-butyl
ABD	-F	-n-propyl
ABE	$-CH_3$	-H
ABF	$-CH_3$	-*iso*-butyl
ABG	$-CH_3$	-*tert*-butyl
ABH	$-CH_3$	-*sec*-butyl
ABI	$-CH_3$	-cyclohexyl
ABJ	$-CH_3$	-*tert*-butoxy
ABK	$-CH_3$	-*iso*-propoxy
ABL	$-CH_3$	$-CF_3$
ABM	$-CH_3$	$-CH_2CF_3$
ABN	$-CH_3$	$-OCF_3$
ABO	$-CH_3$	-Cl
ABP	$-CH_3$	-Br
ABQ	$-CH_3$	-I
ABR	$-CH_3$	-n-butyl
ABS	$-CH_3$	-n-propyl
ABT	$-CF_3$	-H
ABU	$-CF_3$	-*tert*-butyl
ABV	$-CF_3$	-*iso*-butyl
ABW	$-CF_3$	-*sec*-butyl
ABX	$-CF_3$	-cyclohexyl
ABY	$-CF_3$	-*tert*-butoxy
ABZ	$-CF_3$	-*iso*-propoxy
ACA	$-CF_3$	$-CF_3$
ACB	$-CF_3$	$-CH_2CF_3$
ACC	$-CF_3$	$-OCF_3$
ACD	$-CF_3$	-Cl
ACE	$-CF_3$	-Br
ACF	$-CF_3$	-I
ACG	$-CF_3$	-n-butyl
ACH	$-CF_3$	-n-propyl
ACI	$-CHF_2$	-*tert*-butyl
ACJ	$-CHF_2$	-H
ACK	$-CHF_2$	-*iso*-butyl
ACL	$-CHF_2$	-*sec*-butyl
ACM	$-CHF_2$	-cyclohexyl
CAN	$-CHF_2$	-*tert*-butoxy
ACO	$-CHF_2$	-*iso*-propoxy
ACP	$-CHF_2$	$-CF_3$
ACQ	$-CHF_2$	$-CH_2CF_3$
ACR	$-CHF_2$	$-OCF_3$
ACS	$-CHF_2$	-Cl
ACT	$-CHF_2$	-Br
ACU	$-CHF_2$	-I
ACV	$-CHF_2$	-n-butyl

ACW	$-CHF_2$	-n-propyl
ACX	-OH	-H
ACY	-OH	-*tert*-butyl
ACZ	-OH	-*iso*-butyl
ADA	-OH	-*sec*-butyl
ADB	-OH	-cyclohexyl
ADC	-OH	-*tert*-butoxy
ADD	-OH	-*iso*-propoxy
ADE	-OH	$-CF_3$
ADF	-OH	$-CH_2CF_3$
ADG	-OH	$-OCF_3$
ADH	-OH	-Cl
ADI	-OH	-Br
ADJ	-OH	-I
ADK	-OH	-n-butyl
ADL	-OH	-n-propyl
ADM	$-NO_2$	-H
AND	$-NO_2$	-*tert*-butyl
ADO	$-NO_2$	-*iso*-butyl
ADP	$-NO_2$	-*sec*-butyl
ADQ	$-NO_2$	-cyclohexyl
ADR	$-NO_2$	-*tert*-butoxy
ADS	$-NO_2$	-*iso*-propoxy
ADT	$-NO_2$	$-CF_3$
ADU	$-NO_2$	$-CH_2CF_3$
ADV	$-NO_2$	$-OCF_3$
ADW	$-NO_2$	-Cl
ADX	$-NO_2$	-Br
ADY	$-NO_2$	-I
ADZ	$-NO_2$	-n-butyl
AEA	$-NO_2$	-n-propyl
AEB	-CN	-H
AEC	-CN	-*tert*-butyl
AED	-CN	-*iso*-butyl
AEE	-CN	-*sec*-butyl
AEF	-CN	-cyclohexyl
AEG	-CN	-*tert*-butoxy
AEH	-CN	-*iso*-propoxy
AEI	-CN	$-CF_3$
AEJ	-CN	$-CH_2CF_3$
AEK	-CN	$-OCF_3$
AEL	-CN	-Cl
AEM	-CN	-Br
AEN	-CN	-I
AEO	-CN	-n-butyl
AEP	-CN	-n-propyl
AEQ	-Br	-H
AER	-Br	-*tert*-butyl

AES	-Br	-*iso*-butyl
AET	-Br	-*sec*-butyl
AEU	-Br	-cyclohexyl
AEV	-Br	-*tert*-butoxy
AEW	-Br	-*iso*-propoxy
AEX	-Br	$-CF_3$
AEY	-Br	$-CH_2CF_3$
AEZ	-Br	$-OCF_3$
AFA	-Br	-Cl
AFB	-Br	-Br
AFC	-Br	-I
AFD	-Br	-n-butyl
AFE	-Br	-n-propyl
AFF	-I	-*tert*-butyl
AFG	-I	-H
AFH	-I	-*iso*-butyl
AFI	-I	-*sec*-butyl
AFJ	-I	-cyclohexyl
AFK	-I	-*tert*-butoxy
AFL	-I	-*iso*-propoxy
AFM	-I	$-CF_3$
AFN	-I	$-CH_2CF_3$
AFO	-I	$-OCF_3$
AFP	-I	-Cl
AFQ	-I	-Br
AFR	-I	-I
AFS	-I	-n-butyl
AFT	-I	-n-propyl

Table 2



(IIb)

and pharmaceutically acceptable salts thereof, where:

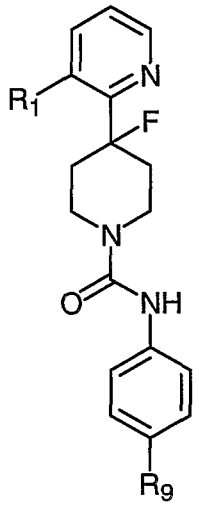
Compound	R_1	R_9
AFU	-Cl	-H
AFV	-Cl	-*tert*-butyl
AFW	-Cl	-*iso*-butyl
AFX	-Cl	-*sec*-butyl
AFY	-Cl	-cyclohexyl
AFZ	-Cl	-*tert*-butoxy
AGA	-Cl	-*iso*-propoxy
AGB	-Cl	$-CF_3$
AGC	-Cl	$-CH_2CF_3$
AGD	-Cl	$-OCF_3$
AGE	-Cl	-Cl
AGF	-Cl	-Br
AGG	-Cl	-I
AGH	-Cl	-n-butyl
AGI	-Cl	-n-propyl
AGJ	-F	-H
AGK	-F	-*tert*-butyl
AGL	-F	-*iso*-butyl
AGM	-F	-*sec*-butyl
AGN	-F	-cyclohexyl
AGO	-F	-*tert*-butoxy
AGP	-F	-*iso*-propoxy
AGQ	-F	$-CF_3$
AGR	-F	$-CH_2CF_3$
AGS	-F	$-OCF_3$
AGT	-F	-Cl

AGU	-F	-Br
AGV	-F	-I
AGW	-F	-n-butyl
AGX	-F	-n-propyl
AGY	$-CH_3$	-H
AGZ	$-CH_3$	-*tert*-butyl
AHA	$-CH_3$	-*iso*-butyl
AHB	$-CH_3$	-*sec*-butyl
AHC	$-CH_3$	-cyclohexyl
AHD	$-CH_3$	-*tert*-butoxy
AHE	$-CH_3$	-*iso*-propoxy
AHF	$-CH_3$	$-CF_3$
AHG	$-CH_3$	$-CH_2CF_3$
AHH	$-CH_3$	$-OCF_3$
AHI	$-CH_3$	-Cl
AHJ	$-CH_3$	-Br
AHK	$-CH_3$	-I
AHL	$-CH_3$	-n-butyl
AHM	$-CH_3$	-n-propyl
AHN	$-CF_3$	-H
AHO	$-CF_3$	-*tert*-butyl
AHP	$-CF_3$	-*iso*-butyl
AHQ	$-CF_3$	-*sec*-butyl
AHR	$-CF_3$	-cyclohexyl
AHS	$-CF_3$	-*tert*-butoxy
AHT	$-CF_3$	-*iso*-propoxy
AHU	$-CF_3$	$-CF_3$
AHV	$-CF_3$	$-CH_2CF_3$
AHW	$-CF_3$	$-OCF_3$
AHX	$-CF_3$	-Cl
AHY	$-CF_3$	-Br
AHZ	$-CF_3$	-I
AIA	$-CF_3$	-n-butyl
AIB	$-CF_3$	-n-propyl
AIC	$-CHF_2$	-*tert*-butyl
AID	$-CHF_2$	-H
AIE	$-CHF_2$	-*iso*-butyl
AIF	$-CHF_2$	-*sec*-butyl
AIG	$-CHF_2$	-cyclohexyl
AIH	$-CHF_2$	-*tert*-butoxy
AII	$-CHF_2$	-*iso*-propoxy
AIJ	$-CHF_2$	$-CF_3$
AIK	$-CHF_2$	$-CH_2CF_3$
AIL	$-CHF_2$	$-OCF_3$
AIM	$-CHF_2$	-Cl
AIN	$-CHF_2$	-Br
AIO	$-CHF_2$	-I
AIP	$-CHF_2$	-n-butyl

AIQ	$-CHF_2$	-n-propyl
AIR	-OH	-H
AIS	-OH	-*tert*-butyl
AIT	-OH	-*iso*-butyl
AIU	-OH	-*sec*-butyl
AIV	-OH	-cyclohexyl
AIW	-OH	-*tert*-butoxy
AIX	-OH	-*iso*-propoxy
AIY	-OH	$-CF_3$
AIZ	-OH	$-CH_2CF_3$
AJA	-OH	$-OCF_3$
AJB	-OH	-Cl
AJC	-OH	-Br
AJD	-OH	-I
AJE	-OH	-n-butyl
AJF	-OH	-n-propyl
AJG	$-NO_2$	-H
AJH	$-NO_2$	-*tert*-butyl
AJI	$-NO_2$	-*iso*-butyl
AJJ	$-NO_2$	-*sec*-butyl
AJK	$-NO_2$	-cyclohexyl
AJL	$-NO_2$	-*tert*-butoxy
AJM	$-NO_2$	-*iso*-propoxy
AJN	$-NO_2$	$-CF_3$
AJO	$-NO_2$	$-CH_2CF_3$
AJP	$-NO_2$	$-OCF_3$
AJQ	$-NO_2$	-Cl
AJR	$-NO_2$	-Br
AJS	$-NO_2$	-I
AJT	$-NO_2$	-n-butyl
AJU	$-NO_2$	-n-propyl
AJV	-CN	-H
AJW	-CN	-*tert*-butyl
AJX	-CN	-*iso*-butyl
AJY	-CN	-*sec*-butyl
AJZ	-CN	-cyclohexyl
AKA	-CN	-*tert*-butoxy
AKB	-CN	-*iso*-propoxy
AKC	-CN	$-CF_3$
AKD	-CN	$-CH_2CF_3$
AKE	-CN	$-OCF_3$
AKF	-CN	-Cl
AKG	-CN	-Br
AKH	-CN	-I
AKI	-CN	-n-butyl
AKJ	-CN	-n-propyl
AKK	-Br	-H
AKL	-Br	-*tert*-butyl

AKM	-Br	-*iso*-butyl
AKN	-Br	-*sec*-butyl
AKO	-Br	-cyclohexyl
AKP	-Br	-*tert*-butoxy
AKQ	-Br	-*iso*-propoxy
AKR	-Br	$-CF_3$
AKS	-Br	$-CH_2CF_3$
AKT	-Br	$-OCF_3$
AKU	-Br	-Cl
AKV	-Br	-Br
AKW	-Br	-I
AKX	-Br	-n-butyl
AKY	-Br	-n-propyl
AKZ	-I	-*tert*-butyl
ALA	-I	-H
ALB	-I	-*iso*-butyl
ALC	-I	-*sec*-butyl
ALD	-I	-cyclohexyl
ALE	-I	-*tert*-butoxy
ALF	-I	-*iso*-propoxy
ALG	-I	$-CF_3$
ALH	-I	$-CH_2CF_3$
ALI	-I	$-OCF_3$
ALJ	-I	-Cl
ALK	-I	-Br
ALL	-I	-I
ALM	-I	-n-butyl
ALN	-I	-n-propyl

Table 3



(IIc)

and pharmaceutically acceptable salts thereof, where:

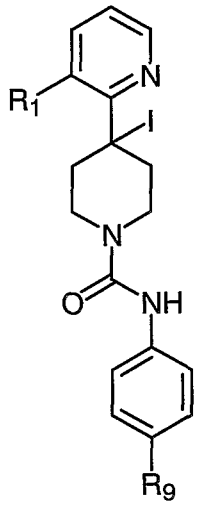
Compound	R_1	R_9
ALO	-Cl	-H
ALP	-Cl	-*tert*-butyl
ALQ	-Cl	-*iso*-butyl
ALR	-Cl	-*sec*-butyl
ALS	-Cl	-cyclohexyl
ALT	-Cl	-*tert*-butoxy
ALU	-Cl	-*iso*-propoxy
ALV	-Cl	$-CF_3$
ALW	-Cl	$-CH_2CF_3$
ALX	-Cl	$-OCF_3$
ALY	-Cl	-Cl
ALZ	-Cl	-Br
AMA	-Cl	-I
AMB	-Cl	-n-butyl
AMC	-Cl	-n-propyl
AMD	-F	-H
AME	-F	-*tert*-butyl
AMF	-F	-*iso*-butyl
AMG	-F	-*sec*-butyl
AMH	-F	-cyclohexyl
AMI	-F	-*tert*-butoxy
AMJ	-F	-*iso*-propoxy
AMK	-F	$-CF_3$
AML	-F	$-CH_2CF_3$
AMM	-F	$-OCF_3$
AMN	-F	-Cl

AMO	-F	-Br
AMP	-F	-I
AMQ	-F	-n-butyl
AMR	-F	-n-propyl
AMS	$-CH_3$	-H
AMT	$-CH_3$	-*tert*-butyl
AMU	$-CH_3$	-*iso*-butyl
AMV	$-CH_3$	-*sec*-butyl
AMW	$-CH_3$	-cyclohexyl
AMX	$-CH_3$	-*tert*-butoxy
AMY	$-CH_3$	-*iso*-propoxy
AMZ	$-CH_3$	$-CF_3$
ANA	$-CH_3$	$-CH_2CF_3$
ANB	$-CH_3$	$-OCF_3$
ANC	$-CH_3$	-Cl
AND	$-CH_3$	-Br
ANE	$-CH_3$	-I
ANF	$-CH_3$	-n-butyl
ANG	$-CH_3$	-n-propyl
ANH	$-CF_3$	-H
ANI	$-CF_3$	-*tert*-butyl
ANJ	$-CF_3$	-*iso*-butyl
ANK	$-CF_3$	-*sec*-butyl
ANL	$-CF_3$	-cyclohexyl
ANM	$-CF_3$	-*tert*-butoxy
ANN	$-CF_3$	-*iso*-propoxy
ANO	$-CF_3$	$-CF_3$
ANP	$-CF_3$	$-CH_2CF_3$
ANQ	$-CF_3$	$-OCF_3$
ANR	$-CF_3$	-Cl
ANS	$-CF_3$	-Br
ANT	$-CF_3$	-I
ANU	$-CF_3$	-n-butyl
ANV	$-CF_3$	-n-propyl
ANW	$-CHF_2$	-*tert*-butyl
ANX	$-CHF_2$	-H
ANY	$-CHF_2$	-*iso*-butyl
ANZ	$-CHF_2$	-*sec*-butyl
AOA	$-CHF_2$	-cyclohexyl
AOB	$-CHF_2$	-*tert*-butoxy
AOC	$-CHF_2$	-*iso*-propoxy
AOD	$-CHF_2$	$-CF_3$
AOE	$-CHF_2$	$-CH_2CF_3$
AOF	$-CHF_2$	$-OCF_3$
AOG	$-CHF_2$	-Cl
AOH	$-CHF_2$	-Br
AOI	$-CHF_2$	-I
AOJ	$-CHF_2$	-n-butyl

AOK	$-CHF_2$	-n-propyl
AOL	-OH	-H
AOM	-OH	-*tert*-butyl
AON	-OH	-*iso*-butyl
AOO	-OH	-*sec*-butyl
AOP	-OH	-cyclohexyl
AOQ	-OH	-*tert*-butoxy
AOR	-OH	-*iso*-propoxy
AOS	-OH	$-CF_3$
AOT	-OH	$-CH_2CF_3$
AOU	-OH	$-OCF_3$
AOV	-OH	-Cl
AOW	-OH	-Br
AOX	-OH	-I
AOY	-OH	-n-butyl
AOZ	-OH	-n-propyl
APA	$-NO_2$	-H
APB	$-NO_2$	-*tert*-butyl
APC	$-NO_2$	-*iso*-butyl
APD	$-NO_2$	-*sec*-butyl
APE	$-NO_2$	-cyclohexyl
APF	$-NO_2$	-*tert*-butoxy
APG	$-NO_2$	-*iso*-propoxy
APH	$-NO_2$	$-CF_3$
API	$-NO_2$	$-CH_2CF_3$
APJ	$-NO_2$	$-OCF_3$
APK	$-NO_2$	-Cl
APL	$-NO_2$	-Br
APM	$-NO_2$	-I
APN	$-NO_2$	-n-butyl
APO	$-NO_2$	-n-propyl
APP	-CN	-H
APQ	-CN	-*tert*-butyl
APR	-CN	-*iso*-butyl
APS	-CN	-*sec*-butyl
APT	-CN	-cyclohexyl
APU	-CN	-*tert*-butoxy
APV	-CN	-*iso*-propoxy
APW	-CN	$-CF_3$
APX	-CN	$-CH_2CF_3$
APY	-CN	$-OCF_3$
APZ	-CN	-Cl
AQA	-CN	-Br
AQB	-CN	-I
AQC	-CN	-n-butyl
AQD	-CN	-n-propyl
AQE	-Br	-H
AQF	-Br	-*tert*-butyl

AQG	-Br	-*iso*-butyl
AQH	-Br	-*sec*-butyl
AQI	-Br	-cyclohexyl
AQJ	-Br	-*tert*-butoxy
AQK	-Br	-*iso*-propoxy
AQL	-Br	$-CF_3$
AQM	-Br	$-CH_2CF_3$
AQN	-Br	$-OCF_3$
AQO	-Br	-Cl
AQP	-Br	-Br
AQQ	-Br	-I
AQR	-Br	-n-butyl
AQS	-Br	-n-propyl
AQT	-I	-*tert*-butyl
AQU	-I	-H
AQV	-I	-*iso*-butyl
AQW	-I	-*sec*-butyl
AQX	-I	-cyclohexyl
AQY	-I	-*tert*-butoxy
AQZ	-I	-*iso*-propoxy
ARA	-I	$-CF_3$
ARB	-I	$-CH_2CF_3$
ARC	-I	$-OCF_3$
ARD	-I	-Cl
ARE	-I	-Br
ARF	-I	-I
ARG	-I	-n-butyl
ARH	-I	-n-propyl

Table 4



(IId)

and pharmaceutically acceptable salts thereof, where:

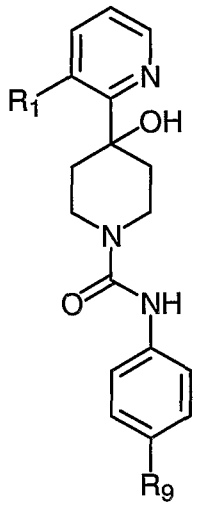
Compound	R_1	R_9
ARI	-Cl	-H
ARJ	-Cl	-*tert*-butyl
ARK	-Cl	-*iso*-butyl
ARL	-Cl	-*sec*-butyl
ARM	-Cl	-cyclohexyl
ARN	-Cl	-*tert*-butoxy
ARO	-Cl	-*iso*-propoxy
ARP	-Cl	$-CF_3$
ARQ	-Cl	$-CH_2CF_3$
ARR	-Cl	$-OCF_3$
ARS	-Cl	-Cl
ART	-Cl	-Br
ARU	-Cl	-I
ARV	-Cl	-n-butyl
ARW	-Cl	-n-propyl
ARX	-F	-H
ARY	-F	-*tert*-butyl
ARZ	-F	-*iso*-butyl
ASA	-F	-*sec*-butyl
ASB	-F	-cyclohexyl
ASC	-F	-*tert*-butoxy
ASD	-F	-*iso*-propoxy
ASE	-F	$-CF_3$
ASF	-F	$-CH_2CF_3$
ASG	-F	$-OCF_3$
ASH	-F	-Cl

ASI	-F	-Br
ASJ	-F	-I
ASK	-F	-n-butyl
ASL	-F	-n-propyl
ASM	$-CH_3$	-H
ASN	$-CH_3$	-*tert*-butyl
ASO	$-CH_3$	-*iso*-butyl
ASP	$-CH_3$	-*sec*-butyl
ASQ	$-CH_3$	-cyclohexyl
ASR	$-CH_3$	-*tert*-butoxy
ASS	$-CH_3$	-*iso*-propoxy
AST	$-CH_3$	$-CF_3$
ASU	$-CH_3$	$-CH_2CF_3$
ASV	$-CH_3$	$-OCF_3$
ASW	$-CH_3$	-Cl
ASX	$-CH_3$	-Br
ASY	$-CH_3$	-I
ASZ	$-CH_3$	-n-butyl
ATA	$-CH_3$	-n-propyl
ATB	$-CF_3$	-H
ATC	$-CF_3$	-*tert*-butyl
ATD	$-CF_3$	-*iso*-butyl
ATE	$-CF_3$	-*sec*-butyl
ATF	$-CF_3$	-cyclohexyl
ATG	$-CF_3$	-*tert*-butoxy
ATH	$-CF_3$	-*iso*-propoxy
ATI	$-CF_3$	$-CF_3$
ATJ	$-CF_3$	$-CH_2CF_3$
ATK	$-CF_3$	$-OCF_3$
ATL	$-CF_3$	-Cl
ATM	$-CF_3$	-Br
ATN	$-CF_3$	-I
ATO	$-CF_3$	-n-butyl
ATP	$-CF_3$	-n-propyl
ATQ	$-CHF_2$	-*tert*-butyl
ATR	$-CHF_2$	-H
ATS	$-CHF_2$	-*iso*-butyl
ATT	$-CHF_2$	-*sec*-butyl
ATU	$-CHF_2$	-cyclohexyl
ATV	$-CHF_2$	-*tert*-butoxy
ATW	$-CHF_2$	-*iso*-propoxy
ATX	$-CHF_2$	$-CF_3$
ATY	$-CHF_2$	$-CH_2CF_3$
ATZ	$-CHF_2$	$-OCF_3$
AUA	$-CHF_2$	-Cl
AUB	$-CHF_2$	-Br
AUC	$-CHF_2$	-I
AUD	$-CHF_2$	-n-butyl

AUE	$-CHF_2$	-n-propyl
AUF	-OH	-H
AUG	-OH	-*tert*-butyl
AUH	-OH	-*iso*-butyl
AUI	-OH	-*sec*-butyl
AUJ	-OH	-cyclohexyl
AUK	-OH	-*tert*-butoxy
AUL	-OH	-*iso*-propoxy
AUM	-OH	$-CF_3$
AUN	-OH	$-CH_2CF_3$
AUO	-OH	$-OCF_3$
AUP	-OH	-Cl
AUQ	-OH	-Br
AUR	-OH	-I
AUS	-OH	-n-butyl
AUT	-OH	-n-propyl
AUU	$-NO_2$	-H
AUV	$-NO_2$	-*tert*-butyl
AUW	$-NO_2$	-*iso*-butyl
AUX	$-NO_2$	-*sec*-butyl
AUY	$-NO_2$	-cyclohexyl
AUZ	$-NO_2$	-*tert*-butoxy
AVA	$-NO_2$	-*iso*-propoxy
AVB	$-NO_2$	$-CF_3$
AVC	$-NO_2$	$-CH_2CF_3$
AVD	$-NO_2$	$-OCF_3$
AVE	$-NO_2$	-Cl
AVF	$-NO_2$	-Br
AVG	$-NO_2$	-I
AVH	$-NO_2$	-n-butyl
AVI	$-NO_2$	-n-propyl
AVJ	-CN	-H
AVK	-CN	-*tert*-butyl
AVL	-CN	-*iso*-butyl
AVM	-CN	-*sec*-butyl
AVN	-CN	-cyclohexyl
AVO	-CN	-*tert*-butoxy
AVP	-CN	-*iso*-propoxy
AVQ	-CN	$-CF_3$
AVR	-CN	$-CH_2CF_3$
AVS	-CN	$-OCF_3$
AVT	-CN	-Cl
AVU	-CN	-Br
AVV	-CN	-I
AVW	-CN	-n-butyl
AVX	-CN	-n-propyl
AVY	-Br	-H
AVZ	-Br	-*tert*-butyl

AWA	-Br	-*iso*-butyl
AWB	-Br	-*sec*-butyl
AWC	-Br	-cyclohexyl
AWD	-Br	-*tert*-butoxy
AWE	-Br	-*iso*-propoxy
AWF	-Br	$-CF_3$
AWG	-Br	$-CH_2CF_3$
AWH	-Br	$-OCF_3$
AWI	-Br	-Cl
AWJ	-Br	-Br
AWK	-Br	-I
AWL	-Br	-n-butyl
AWM	-Br	-n-propyl
AWN	-I	-*tert*-butyl
AWO	-I	-H
AWP	-I	-*iso*-butyl
AWQ	-I	-*sec*-butyl
AWR	-I	-cyclohexyl
AWS	-I	-*tert*-butoxy
AWT	-I	-*iso*-propoxy
AWU	-I	$-CF_3$
AWV	-I	$-CH_2CF_3$
AWW	-I	$-OCF_3$
AWX	-I	-Cl
AWY	-I	-Br
AWZ	-I	-I
AXA	-I	-n-butyl
AXB	-I	-n-propyl

Table 5



(IIe)

and pharmaceutically acceptable salts thereof, where:

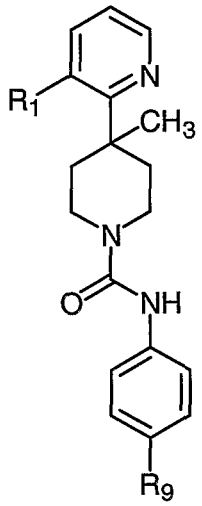
Compound	R_1	R_9
AXC	-Cl	-H
AXD	-Cl	-*tert*-butyl
AXE	-Cl	-*iso*-butyl
AXF	-Cl	-*sec*-butyl
AXG	-Cl	-cyclohexyl
AXH	-Cl	-*tert*-butoxy
AXI	-Cl	-*iso*-propoxy
AXJ	-Cl	$-CF_3$
AXK	-Cl	$-CH_2CF_3$
AXL	-Cl	$-OCF_3$
AXM	-Cl	-Cl
AXN	-Cl	-Br
AXO	-Cl	-I
AXP	-Cl	-n-butyl
AXQ	-Cl	-n-propyl
AXR	-F	-H
AXS	-F	-*tert*-butyl
AXT	-F	-*iso*-butyl
AXU	-F	-*sec*-butyl
AXV	-F	-cyclohexyl
AXW	-F	-*tert*-butoxy
AXX	-F	-*iso*-propoxy
AXY	-F	$-CF_3$
AXZ	-F	$-CH_2CF_3$
AYA	-F	$-OCF_3$
AYB	-F	-Cl

AYC	-F	-Br
AYD	-F	-I
AYE	-F	-n-butyl
AYF	-F	-n-propyl
AYG	$-CH_3$	-H
AYH	$-CH_3$	-*tert*-butyl
AYI	$-CH_3$	-*iso*-butyl
AYJ	$-CH_3$	-*sec*-butyl
AYK	$-CH_3$	-cyclohexyl
AYL	$-CH_3$	-*tert*-butoxy
AYM	$-CH_3$	-*iso*-propoxy
AYN	$-CH_3$	$-CF_3$
AYO	$-CH_3$	$-CH_2CF_3$
AYP	$-CH_3$	$-OCF_3$
AYQ	$-CH_3$	-Cl
AYR	$-CH_3$	-Br
AYS	$-CH_3$	-I
AYT	$-CH_3$	-n-butyl
AYU	$-CH_3$	-n-propyl
AYV	$-CF_3$	-H
AYW	$-CF_3$	-*tert*-butyl
AYX	$-CF_3$	-*iso*-butyl
AYY	$-CF_3$	-*sec*-butyl
AYZ	$-CF_3$	-cyclohexyl
AZA	$-CF_3$	-*tert*-butoxy
AZB	$-CF_3$	-*iso*-propoxy
AZC	$-CF_3$	$-CF_3$
AZD	$-CF_3$	$-CH_2CF_3$
AZE	$-CF_3$	$-OCF_3$
AZF	$-CF_3$	-Cl
AZG	$-CF_3$	-Br
AZH	$-CF_3$	-I
AZI	$-CF_3$	-n-butyl
AZJ	$-CF_3$	-n-propyl
AZK	$-CHF_2$	-*tert*-butyl
AZL	$-CHF_2$	-H
AZM	$-CHF_2$	-*iso*-butyl
AZN	$-CHF_2$	-*sec*-butyl
AZO	$-CHF_2$	-cyclohexyl
AZP	$-CHF_2$	-*tert*-butoxy
AZQ	$-CHF_2$	-*iso*-propoxy
AZR	$-CHF_2$	$-CF_3$
AZS	$-CHF_2$	$-CH_2CF_3$
AZT	$-CHF_2$	$-OCF_3$
AZU	$-CHF_2$	-Cl
AZV	$-CHF_2$	-Br
AZW	$-CHF_2$	-I
AZX	$-CHF_2$	-n-butyl

AZY	$-CHF_2$	-n-propyl
AZZ	-OH	-H
BAA	-OH	-*tert*-butyl
BAB	-OH	-*iso*-butyl
BAC	-OH	-*sec*-butyl
BAD	-OH	-cyclohexyl
BAE	-OH	-*tert*-butoxy
BAF	-OH	-*iso*-propoxy
BAG	-OH	$-CF_3$
BAH	-OH	$-CH_2CF_3$
BAI	-OH	$-OCF_3$
BAJ	-OH	-Cl
BAK	-OH	-Br
BAL	-OH	-I
BAM	-OH	-n-butyl
BAN	-OH	-n-propyl
BAO	$-NO_2$	-H
BAP	$-NO_2$	-*tert*-butyl
BAQ	$-NO_2$	-*iso*-butyl
BAR	$-NO_2$	-*sec*-butyl
BAS	$-NO_2$	-cyclohexyl
BAT	$-NO_2$	-*tert*-butoxy
BAU	$-NO_2$	-*iso*-propoxy
BAV	$-NO_2$	$-CF_3$
BAW	$-NO_2$	$-CH_2CF_3$
BAX	$-NO_2$	$-OCF_3$
BAY	$-NO_2$	-Cl
BAZ	$-NO_2$	-Br
BBA	$-NO_2$	-I
BBB	$-NO_2$	-n-butyl
BBC	$-NO_2$	-n-propyl
BBD	-CN	-H
BBE	-CN	-*tert*-butyl
BBF	-CN	-*iso*-butyl
BBG	-CN	-*sec*-butyl
BBH	-CN	-cyclohexyl
BBI	-CN	-*tert*-butoxy
BBJ	-CN	-*iso*-propoxy
BBK	-CN	$-CF_3$
BBL	-CN	$-CH_2CF_3$
BBM	-CN	$-OCF_3$
BBN	-CN	-Cl
BBO	-CN	-Br
BBP	-CN	-I
BBQ	-CN	-n-butyl
BBR	-CN	-n-propyl
BBS	-Br	-H
BBT	-Br	-*tert*-butyl

BBU	-Br	-*iso*-butyl
BBV	-Br	-*sec*-butyl
BBW	-Br	-cyclohexyl
BBX	-Br	-*tert*-butoxy
BBY	-Br	-*iso*-propoxy
BBZ	-Br	$-CF_3$
BCA	-Br	$-CH_2CF_3$
BCB	-Br	$-OCF_3$
BCC	-Br	-Cl
BCD	-Br	-Br
BCE	-Br	-I
BCF	-Br	-n-butyl
BCG	-Br	-n-propyl
BCH	-I	-*tert*-butyl
BCI	-I	-H
BCJ	-I	-*iso*-butyl
BCK	-I	-*sec*-butyl
BCL	-I	-cyclohexyl
BCM	-I	-*tert*-butoxy
BCN	-I	-*iso*-propoxy
BCO	-I	$-CF_3$
BCP	-I	$-CH_2CF_3$
BCQ	-I	$-OCF_3$
BCR	-I	-Cl
BCS	-I	-Br
BCT	-I	-I
BCU	-I	-n-butyl
BCV	-I	-n-propyl

Table 6



(IIf)

and pharmaceutically acceptable salts thereof, where:

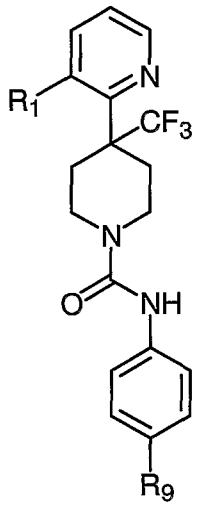
Compound	R_1	R_9
BCW	-Cl	-H
BCX	-Cl	-*tert*-butyl
BCY	-Cl	-*iso*-butyl
BCZ	-Cl	-*sec*-butyl
BDA	-Cl	-cyclohexyl
BDB	-Cl	-*tert*-butoxy
BDC	-Cl	-*iso*-propoxy
BDD	-Cl	$-CF_3$
BDE	-Cl	$-CH_2CF_3$
BDF	-Cl	$-OCF_3$
BDG	-Cl	-Cl
BDH	-Cl	-Br
BDI	-Cl	-I
BDJ	-Cl	-n-butyl
BDK	-Cl	-n-propyl
BDL	-F	-H
BDM	-F	-*tert*-butyl
BDN	-F	-*iso*-butyl
BDO	-F	-*sec*-butyl
BDP	-F	-cyclohexyl
BDQ	-F	-*tert*-butoxy
BDR	-F	-*iso*-propoxy
BDS	-F	$-CF_3$
BDT	-F	$-CH_2CF_3$
BDU	-F	$-OCF_3$
BDV	-F	-Cl

BDW	-F	-Br
BDX	-F	-I
BDY	-F	-n-butyl
BDZ	-F	-n-propyl
BEA	$-CH_3$	-H
BEB	$-CH_3$	-*tert*-butyl
BEC	$-CH_3$	-*iso*-butyl
BED	$-CH_3$	-*sec*-butyl
BEE	$-CH_3$	-cyclohexyl
BEF	$-CH_3$	-*tert*-butoxy
BEG	$-CH_3$	-*iso*-propoxy
BEH	$-CH_3$	$-CF_3$
BEI	$-CH_3$	$-CH_2CF_3$
BEJ	$-CH_3$	$-OCF_3$
BEK	$-CH_3$	-Cl
BEL	$-CH_3$	-Br
BEM	$-CH_3$	-I
BEN	$-CH_3$	-n-butyl
BEO	$-CH_3$	-n-propyl
BEP	$-CF_3$	-H
BEQ	$-CF_3$	-*tert*-butyl
BER	$-CF_3$	-*iso*-butyl
BES	$-CF_3$	-*sec*-butyl
BET	$-CF_3$	-cyclohexyl
BEU	$-CF_3$	-*tert*-butoxy
BEV	$-CF_3$	-*iso*-propoxy
BEW	$-CF_3$	$-CF_3$
BEX	$-CF_3$	$-CH_2CF_3$
BEY	$-CF_3$	$-OCF_3$
BEZ	$-CF_3$	-Cl
BFA	$-CF_3$	-Br
BFB	$-CF_3$	-I
BFC	$-CF_3$	-n-butyl
BFD	$-CF_3$	-n-propyl
BFE	$-CHF_2$	-*tert*-butyl
BFF	$-CHF_2$	-H
BFG	$-CHF_2$	-*iso*-butyl
BFH	$-CHF_2$	-*sec*-butyl
BFI	$-CHF_2$	-cyclohexyl
BFJ	$-CHF_2$	-*tert*-butoxy
BFK	$-CHF_2$	-*iso*-propoxy
BFL	$-CHF_2$	$-CF_3$
BFM	$-CHF_2$	$-CH_2CF_3$
BFN	$-CHF_2$	$-OCF_3$
BFO	$-CHF_2$	-Cl
BFP	$-CHF_2$	-Br
BFQ	$-CHF_2$	-I
BFR	$-CHF_2$	-n-butyl

BFS	$-CHF_2$	-n-propyl
BFT	-OH	-H
BFU	-OH	-*tert*-butyl
BFV	-OH	-*iso*-butyl
BFW	-OH	-*sec*-butyl
BFX	-OH	-cyclohexyl
BFY	-OH	-*tert*-butoxy
BFZ	-OH	-*iso*-propoxy
BGA	-OH	$-CF_3$
BGB	-OH	$-CH_2CF_3$
BGC	-OH	$-OCF_3$
BGD	-OH	-Cl
BGE	-OH	-Br
BGF	-OH	-I
BGG	-OH	-n-butyl
BGH	-OH	-n-propyl
BGI	$-NO_2$	-H
BGJ	$-NO_2$	-*tert*-butyl
BGK	$-NO_2$	-*iso*-butyl
BGL	$-NO_2$	-*sec*-butyl
BGM	$-NO_2$	-cyclohexyl
BGN	$-NO_2$	-*tert*-butoxy
BGO	$-NO_2$	-*iso*-propoxy
BGP	$-NO_2$	$-CF_3$
BGQ	$-NO_2$	$-CH_2CF_3$
BGR	$-NO_2$	$-OCF_3$
BGS	$-NO_2$	-Cl
BGT	$-NO_2$	-Br
BGU	$-NO_2$	-I
BGV	$-NO_2$	-n-butyl
BGW	$-NO_2$	-n-propyl
BGX	-CN	-H
BGY	-CN	-*tert*-butyl
BGZ	-CN	-*iso*-butyl
BHA	-CN	-*sec*-butyl
BHB	-CN	-cyclohexyl
BHC	-CN	-*tert*-butoxy
BHD	-CN	-*iso*-propoxy
BHE	-CN	$-CF_3$
BHF	-CN	$-CH_2CF_3$
BHG	-CN	$-OCF_3$
BHH	-CN	-Cl
BHI	-CN	-Br
BHJ	-CN	-I
BHK	-CN	-n-butyl
BHL	-CN	-n-propyl
BHM	-Br	-H
BHN	-Br	-*tert*-butyl

BHO	-Br	-*iso*-butyl
BHP	-Br	-*sec*-butyl
BHQ	-Br	-cyclohexyl
BHR	-Br	-*tert*-butoxy
BHS	-Br	-*iso*-propoxy
BHT	-Br	$-CF_3$
BHU	-Br	$-CH_2CF_3$
BHV	-Br	$-OCF_3$
BHW	-Br	-Cl
BHX	-Br	-Br
BHY	-Br	-I
BHZ	-Br	-n-butyl
BIA	-Br	-n-propyl
BIB	-I	-*tert*-butyl
BIC	-I	-H
BID	-I	-*iso*-butyl
BIE	-I	-*sec*-butyl
BIF	-I	-cyclohexyl
BIG	-I	-*tert*-butoxy
BIH	-I	-*iso*-propoxy
BII	-I	$-CF_3$
BIJ	-I	$-CH_2CF_3$
BIK	-I	$-OCF_3$
BIL	-I	-Cl
BIM	-I	-Br
BIN	-I	-I
BIO	-I	-n-butyl
BIP	-I	-n-propyl

Table 7



(IIg)

and pharmaceutically acceptable salts thereof, where:

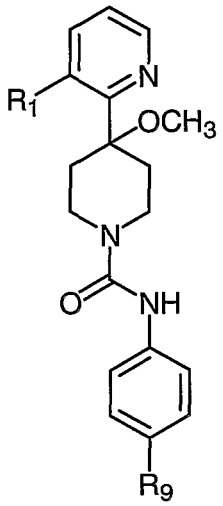
Compound	R_1	R_9
BIQ	-Cl	-H
BIR	-Cl	-*tert*-butyl
BIS	-Cl	-*iso*-butyl
BIT	-Cl	-*sec*-butyl
BIU	-Cl	-cyclohexyl
BIV	-Cl	-*tert*-butoxy
BIW	-Cl	-*iso*-propoxy
BIX	-Cl	$-CF_3$
BIY	-Cl	$-CH_2CF_3$
BIZ	-Cl	$-OCF_3$
BJA	-Cl	-Cl
BJB	-Cl	-Br
BJC	-Cl	-I
BJD	-Cl	-n-butyl
BJE	-Cl	-n-propyl
BJF	-F	-H
BJG	-F	-*tert*-butyl
BJH	-F	-*iso*-butyl
BJI	-F	-*sec*-butyl
BJJ	-F	-cyclohexyl
BJK	-F	-*tert*-butoxy
BJL	-F	-*iso*-propoxy
BJM	-F	$-CF_3$
BJN	-F	$-CH_2CF_3$
BJO	-F	$-OCF_3$
BJP	-F	-Cl

BJQ	-F	-Br
BJR	-F	-I
BJS	-F	-n-butyl
BJT	-F	-n-propyl
BJU	$-CH_3$	-H
BJV	$-CH_3$	-*tert*-butyl
BJW	$-CH_3$	-*iso*-butyl
BJX	$-CH_3$	-*sec*-butyl
BJY	$-CH_3$	-cyclohexyl
BJZ	$-CH_3$	-*tert*-butoxy
BKA	$-CH_3$	-*iso*-propoxy
BKB	$-CH_3$	$-CF_3$
BKC	$-CH_3$	$-CH_2CF_3$
BKD	$-CH_3$	$-OCF_3$
BKE	$-CH_3$	-Cl
BKF	$-CH_3$	-Br
BKG	$-CH_3$	-I
BKH	$-CH_3$	-n-butyl
BKI	$-CH_3$	-n-propyl
BKJ	$-CF_3$	-H
BKK	$-CF_3$	-*tert*-butyl
BKL	$-CF_3$	-*iso*-butyl
BKM	$-CF_3$	-*sec*-butyl
BKN	$-CF_3$	-cyclohexyl
BKO	$-CF_3$	-*tert*-butoxy
BKP	$-CF_3$	-*iso*-propoxy
BKQ	$-CF_3$	$-CF_3$
BKR	$-CF_3$	$-CH_2CF_3$
BKS	$-CF_3$	$-OCF_3$
BKT	$-CF_3$	-Cl
BKU	$-CF_3$	-Br
BKV	$-CF_3$	-I
BKW	$-CF_3$	-n-butyl
BKX	$-CF_3$	-n-propyl
BKY	$-CHF_2$	-*tert*-butyl
BKZ	$-CHF_2$	-H
BLA	$-CHF_2$	-*iso*-butyl
BLB	$-CHF_2$	-*sec*-butyl
BLC	$-CHF_2$	-cyclohexyl
BLD	$-CHF_2$	-*tert*-butoxy
BLE	$-CHF_2$	-*iso*-propoxy
BLF	$-CHF_2$	$-CF_3$
BLG	$-CHF_2$	$-CH_2CF_3$
BLH	$-CHF_2$	$-OCF_3$
BLI	$-CHF_2$	-Cl
BLJ	$-CHF_2$	-Br
BLK	$-CHF_2$	-I
BLL	$-CHF_2$	-n-butyl

BLM	$-CHF_2$	-n-propyl
BLN	-OH	-H
BLO	-OH	-*tert*-butyl
BLP	-OH	-*iso*-butyl
BLQ	-OH	-*sec*-butyl
BLR	-OH	-cyclohexyl
BLS	-OH	-*tert*-butoxy
BLT	-OH	-*iso*-propoxy
BLU	-OH	$-CF_3$
BLV	-OH	$-CH_2CF_3$
BLW	-OH	$-OCF_3$
BLX	-OH	-Cl
BLY	-OH	-Br
BLZ	-OH	-I
BMA	-OH	-n-butyl
BMB	-OH	-n-propyl
BMC	$-NO_2$	-H
BMD	$-NO_2$	-*tert*-butyl
BME	$-NO_2$	-*iso*-butyl
BMF	$-NO_2$	-*sec*-butyl
BMG	$-NO_2$	-cyclohexyl
BMH	$-NO_2$	-*tert*-butoxy
BMI	$-NO_2$	-*iso*-propoxy
BMJ	$-NO_2$	$-CF_3$
BMK	$-NO_2$	$-CH_2CF_3$
BML	$-NO_2$	$-OCF_3$
BMM	$-NO_2$	-Cl
BMN	$-NO_2$	-Br
BMO	$-NO_2$	-I
BMP	$-NO_2$	-n-butyl
BMQ	$-NO_2$	-n-propyl
BMR	-CN	-H
BMS	-CN	-*tert*-butyl
BMT	-CN	-*iso*-butyl
BMU	-CN	-*sec*-butyl
BMV	-CN	-cyclohexyl
BMW	-CN	-*tert*-butoxy
BMX	-CN	-*iso*-propoxy
BMY	-CN	$-CF_3$
BMZ	-CN	$-CH_2CF_3$
BNA	-CN	$-OCF_3$
BNB	-CN	-Cl
BNC	-CN	-Br
BND	-CN	-I
BNE	-CN	-n-butyl
BNF	-CN	-n-propyl
BNG	-Br	-H
BNH	-Br	-*tert*-butyl

BNI	-Br	-*iso*-butyl
BNJ	-Br	-*sec*-butyl
BNK	-Br	-cyclohexyl
BNL	-Br	-*tert*-butoxy
BNM	-Br	-*iso*-propoxy
BNN	-Br	$-CF_3$
BNO	-Br	$-CH_2CF_3$
BNP	-Br	$-OCF_3$
BNQ	-Br	-Cl
BNR	-Br	-Br
BNS	-Br	-I
BNT	-Br	-n-butyl
BNU	-Br	-n-propyl
BNV	-I	-*tert*-butyl
BNW	-I	-H
BNX	-I	-*iso*-butyl
BNY	-I	-*sec*-butyl
BNZ	-I	-cyclohexyl
BOA	-I	-*tert*-butoxy
BOB	-I	-*iso*-propoxy
BOC	-I	$-CF_3$
BOD	-I	$-CH_2CF_3$
BOE	-I	$-OCF_3$
BOF	-I	-Cl
BOG	-I	-Br
BOH	-I	-I
BOI	-I	-n-butyl
BOJ	-I	-n-propyl

Table 8



(Ih)

and pharmaceutically acceptable salts thereof, where:

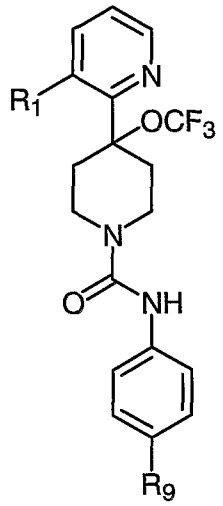
Compound	R_1	R_9
BOK	-Cl	-H
BOL	-Cl	-*tert*-butyl
BOM	-Cl	-*iso*-butyl
BON	-Cl	-*sec*-butyl
BOO	-Cl	-cyclohexyl
BOP	-Cl	-*tert*-butoxy
BOQ	-Cl	-*iso*-propoxy
BOR	-Cl	$-CF_3$
BOS	-Cl	$-CH_2CF_3$
BOT	-Cl	$-OCF_3$
BOU	-Cl	-Cl
BOV	-Cl	-Br
BOW	-Cl	-I
BOX	-Cl	-n-butyl
BOY	-Cl	-n-propyl
BOZ	-F	-H
BPA	-F	-*tert*-butyl
BPB	-F	-*iso*-butyl
BPC	-F	-*sec*-butyl
BPD	-F	-cyclohexyl
BPE	-F	-*tert*-butoxy
BPF	-F	-*iso*-propoxy
BPG	-F	$-CF_3$
BPH	-F	$-CH_2CF_3$
BPI	-F	$-OCF_3$
BPJ	-F	-Cl

BPK	-F	-Br
BPL	-F	-I
BPM	-F	-n-butyl
BPN	-F	-n-propyl
BPO	$-CH_3$	-H
BPP	$-CH_3$	-*tert*-butyl
BPQ	$-CH_3$	-*iso*-butyl
BPR	$-CH_3$	-*sec*-butyl
BPS	$-CH_3$	-cyclohexyl
BPT	$-CH_3$	-*tert*-butoxy
BPU	$-CH_3$	-*iso*-propoxy
BPV	$-CH_3$	$-CF_3$
BPW	$-CH_3$	$-CH_2CF_3$
BPX	$-CH_3$	$-OCF_3$
BPY	$-CH_3$	-Cl
BPZ	$-CH_3$	-Br
BQA	$-CH_3$	-I
BQB	$-CH_3$	-n-butyl
BQC	$-CH_3$	-n-propyl
BQD	$-CF_3$	-H
BQE	$-CF_3$	-*tert*-butyl
BQF	$-CF_3$	-*iso*-butyl
BQG	$-CF_3$	-*sec*-butyl
BQH	$-CF_3$	-cyclohexyl
BQI	$-CF_3$	-*tert*-butoxy
BQJ	$-CF_3$	-*iso*-propoxy
BQK	$-CF_3$	$-CF_3$
BQL	$-CF_3$	$-CH_2CF_3$
BQM	$-CF_3$	$-OCF_3$
BQN	$-CF_3$	-Cl
BQO	$-CF_3$	-Br
BQP	$-CF_3$	-I
BQQ	$-CF_3$	-n-butyl
BQR	$-CF_3$	-n-propyl
BQS	$-CHF_2$	-*tert*-butyl
BQT	$-CHF_2$	-H
BQU	$-CHF_2$	-*iso*-butyl
BQV	$-CHF_2$	-*sec*-butyl
BQW	$-CHF_2$	-cyclohexyl
BQX	$-CHF_2$	-*tert*-butoxy
BQY	$-CHF_2$	-*iso*-propoxy
BQZ	$-CHF_2$	$-CF_3$
BRA	$-CHF_2$	$-CH_2CF_3$
BRB	$-CHF_2$	$-OCF_3$
BRC	$-CHF_2$	-Cl
BRD	$-CHF_2$	-Br
BRE	$-CHF_2$	-I
BRF	$-CHF_2$	-n-butyl

BRG	$-CHF_2$	-n-propyl
BRH	-OH	-H
BRI	-OH	-*tert*-butyl
BRJ	-OH	-*iso*-butyl
BRK	-OH	-*sec*-butyl
BRL	-OH	-cyclohexyl
BRM	-OH	-*tert*-butoxy
BRN	-OH	-*iso*-propoxy
BRO	-OH	$-CF_3$
BRP	-OH	$-CH_2CF_3$
BRQ	-OH	$-OCF_3$
BRR	-OH	-Cl
BRS	-OH	-Br
BRT	-OH	-I
BRU	-OH	-n-butyl
BRV	-OH	-n-propyl
BRW	$-NO_2$	-H
BRX	$-NO_2$	-*tert*-butyl
BRY	$-NO_2$	-*iso*-butyl
BRZ	$-NO_2$	-*sec*-butyl
BSA	$-NO_2$	-cyclohexyl
BSB	$-NO_2$	-*tert*-butoxy
BSC	$-NO_2$	-*iso*-propoxy
BSD	$-NO_2$	$-CF_3$
BSE	$-NO_2$	$-CH_2CF_3$
BSF	$-NO_2$	$-OCF_3$
BSG	$-NO_2$	-Cl
BSH	$-NO_2$	-Br
BSI	$-NO_2$	-I
BSJ	$-NO_2$	-n-butyl
BSK	$-NO_2$	-n-propyl
BSL	-CN	-H
BSM	-CN	-*tert*-butyl
BSN	-CN	-*iso*-butyl
BSO	-CN	-*sec*-butyl
BSP	-CN	-cyclohexyl
BSQ	-CN	-*tert*-butoxy
BSR	-CN	-*iso*-propoxy
BSS	-CN	$-CF_3$
BST	-CN	$-CH_2CF_3$
BSU	-CN	$-OCF_3$
BSV	-CN	-Cl
BSW	-CN	-Br
BSX	-CN	-I
BSY	-CN	-n-butyl
BSZ	-CN	-n-propyl
BTA	-Br	-H
BTB	-Br	-*tert*-butyl

BTC	-Br	-*iso*-butyl
BTD	-Br	-*sec*-butyl
BTE	-Br	-cyclohexyl
BTF	-Br	-*tert*-butoxy
BTG	-Br	-*iso*-propoxy
BTH	-Br	$-CF_3$
BTI	-Br	$-CH_2CF_3$
BTJ	-Br	$-OCF_3$
BTK	-Br	-Cl
BTL	-Br	-Br
BTM	-Br	-I
BTN	-Br	-n-butyl
BTO	-Br	-n-propyl
BTP	-I	-*tert*-butyl
BTQ	-I	-H
BTR	-I	-*iso*-butyl
BTS	-I	-*sec*-butyl
BTT	-I	-cyclohexyl
BTU	-I	-*tert*-butoxy
BTV	-I	-*iso*-propoxy
BTW	-I	$-CF_3$
BTX	-I	$-CH_2CF_3$
BTY	-I	$-OCF_3$
BTZ	-I	-Cl
BUA	-I	-Br
BUB	-I	-I
BUC	-I	-n-butyl
BUD	-I	-n-propyl

Table 9



(IIi)

and pharmaceutically acceptable salts thereof, where:

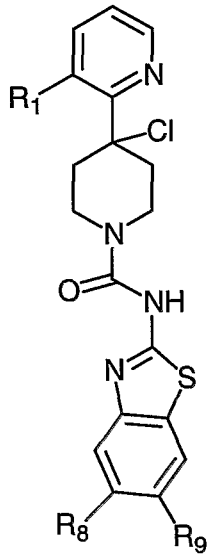
Compound	R_1	R_9
BUE	-Cl	-H
BUF	-Cl	-*tert*-butyl
BUG	-Cl	-*iso*-butyl
BUH	-Cl	-*sec*-butyl
BUI	-Cl	-cyclohexyl
BUJ	-Cl	-*tert*-butoxy
BUK	-Cl	-*iso*-propoxy
BUL	-Cl	$-CF_3$
BUM	-Cl	$-CH_2CF_3$
BUN	-Cl	$-OCF_3$
BUO	-Cl	-Cl
BUP	-Cl	-Br
BUQ	-Cl	-I
BUR	-Cl	-n-butyl
BUS	-Cl	-n-propyl
BUT	-F	-H
BUU	-F	-*tert*-butyl
BUV	-F	-*iso*-butyl
BUW	-F	-*sec*-butyl
BUX	-F	-cyclohexyl
BUY	-F	-*tert*-butoxy
BUZ	-F	-*iso*-propoxy
BVA	-F	$-CF_3$
BVB	-F	$-CH_2CF_3$
BVC	-F	$-OCF_3$
BVD	-F	-Cl

BVE	-F	-Br
BVF	-F	-I
BVG	-F	-n-butyl
BVH	-F	-n-propyl
BVI	$-CH_3$	-H
BVJ	$-CH_3$	-*tert*-butyl
BVK	$-CH_3$	-*iso*-butyl
BVL	$-CH_3$	-*sec*-butyl
BVM	$-CH_3$	-cyclohexyl
BVN	$-CH_3$	-*tert*-butoxy
BVO	$-CH_3$	-*iso*-propoxy
BVP	$-CH_3$	$-CF_3$
BVQ	$-CH_3$	$-CH_2CF_3$
BVR	$-CH_3$	$-OCF_3$
BVS	$-CH_3$	-Cl
BVT	$-CH_3$	-Br
BVU	$-CH_3$	-I
BVV	$-CH_3$	-n-butyl
BVW	$-CH_3$	-n-propyl
BVX	$-CF_3$	-H
BVY	$-CF_3$	-*tert*-butyl
BVZ	$-CF_3$	-*iso*-butyl
BWA	$-CF_3$	-*sec*-butyl
BWB	$-CF_3$	-cyclohexyl
BWC	$-CF_3$	-*tert*-butoxy
BWD	$-CF_3$	-*iso*-propoxy
BWE	$-CF_3$	$-CF_3$
BWF	$-CF_3$	$-CH_2CF_3$
BWG	$-CF_3$	$-OCF_3$
BWH	$-CF_3$	-Cl
BWI	$-CF_3$	-Br
BWJ	$-CF_3$	-I
BWK	$-CF_3$	-n-butyl
BWL	$-CF_3$	-n-propyl
BWM	$-CHF_2$	-*tert*-butyl
BWN	$-CHF_2$	-H
BWO	$-CHF_2$	-*iso*-butyl
BWP	$-CHF_2$	-*sec*-butyl
BWQ	$-CHF_2$	-cyclohexyl
BWR	$-CHF_2$	-*tert*-butoxy
BWS	$-CHF_2$	-*iso*-propoxy
BWT	$-CHF_2$	$-CF_3$
BWU	$-CHF_2$	$-CH_2CF_3$
BWV	$-CHF_2$	$-OCF_3$
BWW	$-CHF_2$	-Cl
BWX	$-CHF_2$	-Br
BWY	$-CHF_2$	-I
BWZ	$-CHF_2$	-n-butyl

BXA	$-CHF_2$	-n-propyl
BXB	-OH	-H
BXC	-OH	-*tert*-butyl
BXD	-OH	-*iso*-butyl
BXE	-OH	-*sec*-butyl
BXF	-OH	-cyclohexyl
BXG	-OH	-*tert*-butoxy
BXH	-OH	-*iso*-propoxy
BXI	-OH	$-CF_3$
BXJ	-OH	$-CH_2CF_3$
BXK	-OH	$-OCF_3$
BXL	-OH	-Cl
BXM	-OH	-Br
BXN	-OH	-I
BXO	-OH	-n-butyl
BXP	-OH	-n-propyl
BXQ	$-NO_2$	-H
BXR	$-NO_2$	-*tert*-butyl
BXS	$-NO_2$	-*iso*-butyl
BXT	$-NO_2$	-*sec*-butyl
BXU	$-NO_2$	-cyclohexyl
BXV	$-NO_2$	-*tert*-butoxy
BXW	$-NO_2$	-*iso*-propoxy
BXX	$-NO_2$	$-CF_3$
BXY	$-NO_2$	$-CH_2CF_3$
BXZ	$-NO_2$	$-OCF_3$
BYA	$-NO_2$	-Cl
BYB	$-NO_2$	-Br
BYC	$-NO_2$	-I
BYD	$-NO_2$	-n-butyl
BYE	$-NO_2$	-n-propyl
BYF	-CN	-H
BYG	-CN	-*tert*-butyl
BYH	-CN	-*iso*-butyl
BYI	-CN	-*sec*-butyl
BYJ	-CN	-cyclohexyl
BYK	-CN	-*tert*-butoxy
BYL	-CN	-*iso*-propoxy
BYM	-CN	$-CF_3$
BYN	-CN	$-CH_2CF_3$
BYO	-CN	$-OCF_3$
BYP	-CN	-Cl
BYQ	-CN	-Br
BYR	-CN	-I
BYS	-CN	-n-butyl
BYT	-CN	-n-propyl
BYU	-Br	-H
BYV	-Br	-*tert*-butyl

BYW	-Br	-*iso*-butyl
BYX	-Br	-*sec*-butyl
BYY	-Br	-cyclohexyl
BYZ	-Br	-*tert*-butoxy
BZA	-Br	-*iso*-propoxy
BZB	-Br	$-CF_3$
BZC	-Br	$-CH_2CF_3$
BZD	-Br	$-OCF_3$
BZE	-Br	-Cl
BZF	-Br	-Br
BZG	-Br	-I
BZH	-Br	-n-butyl
BZI	-Br	-n-propyl
BZJ	-I	-*tert*-butyl
BZK	-I	-H
BZL	-I	-*iso*-butyl
BZM	-I	-*sec*-butyl
BZN	-I	-cyclohexyl
BZO	-I	-*tert*-butoxy
BZP	-I	-*iso*-propoxy
BZQ	-I	$-CF_3$
BZR	-I	$-CH_2CF_3$
BZS	-I	$-OCF_3$
BZT	-I	-Cl
BZU	-I	-Br
BZV	-I	-I
BZW	-I	-n-butyl
BZX	-I	-n-propyl

Table 10



(Ia)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
BZY	-Cl	-Cl	-H
BZZ	-Cl	-Br	-H
CAA	-Cl	-F	-H
CAB	-Cl	$-CH_3$	-H
CAC	-Cl	$-CF_3$	-H
CAD	-Cl	$-OCH_3$	-H
CAE	-Cl	$-OCH_2CH_3$	-H
CAF	-Cl	$-OCF_3$	-H
CAG	-Cl	-*tert*-butyl	-H
CAH	-Cl	-*iso*-propyl	-H
CAI	-Cl	$-CH_3$	$-CH_3$
CAJ	-Cl	-H	-H
CAK	-Cl	-H	$-CH_3$
CAL	-Cl	-H	$-CF_3$
CAM	-Cl	-H	$-OCH_3$
CAN	-Cl	-H	$-OCH_2CH_3$
CAO	-Cl	-H	$-OCF_3$
CAP	-Cl	-H	-*tert*-butyl
CAQ	-Cl	-H	-*iso*-propyl
CAR	-Cl	-H	$-OCF_3$
CAS	-Cl	-H	-*tert*-butyl
CAT	-Cl	-H	-*iso*-propyl
CAU	$-CH_3$	-Cl	-H
CAV	$-CH_3$	-Br	-H

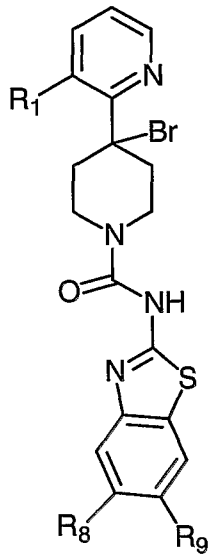
CAW	$-CH_3$	-F	-H
CAX	$-CH_3$	$-CH_3$	-H
CAY	$-CH_3$	$-CF_3$	-H
CAZ	$-CH_3$	$-OCH_3$	-H
CBA	$-CH_3$	$-OCH_2CH_3$	-H
CBB	$-CH_3$	$-OCF_3$	-H
CBC	$-CH_3$	*-tert*-butyl	-H
CBD	$-CH_3$	*-iso*-propyl	-H
CBE	$-CH_3$	$-CH_3$	$-CH_3$
CBF	$-CH_3$	-H	-H
CBG	$-CH_3$	-H	-Cl
CBH	$-CH_3$	-H	-Br
CBI	$-CH_3$	-H	-F
CBJ	$-CH_3$	-H	$-CH_3$
CBK	$-CH_3$	-H	$-CF_3$
CBL	$-CH_3$	-H	$-OCH_3$
CBM	$-CH_3$	-H	$-OCH_2CH_3$
CBN	$-CH_3$	-H	$-OCF_3$
CBO	$-CH_3$	-H	*-tert*-butyl
CBP	$-CH_3$	-H	*-iso*-propyl
CBQ	$-CF_3$	-Cl	-H
CBR	$-CF_3$	-Br	-H
CBS	$-CF_3$	-F	-H
CBT	$-CF_3$	$-CH_3$	-H
CBU	$-CF_3$	$-CF_3$	-H
CBV	$-CF_3$	$-OCH_3$	-H
CBW	$-CF_3$	$-OCH_2CH_3$	-H
CBX	$-CF_3$	$-OCF_3$	-H
CBY	$-CF_3$	*-tert*-butyl	-H
CBZ	$-CF_3$	*-iso*-propyl	-H
CCA	$-CF_3$	$-CH_3$	$-CH_3$
CCB	$-CF_3$	-H	-H
CCC	$-CF_3$	-H	-Cl
CCD	$-CF_3$	-H	-Br
CCE	$-CF_3$	-H	-F
CCF	$-CF_3$	-H	$-CH_3$
CCG	$-CF_3$	-H	$-CF_3$
CCH	$-CF_3$	-H	$-OCH_3$
CCI	$-CF_3$	-H	$-OCH_2CH_3$
CCJ	$-CF_3$	-H	$-OCF_3$
CCK	$-CF_3$	-H	*-tert*-butyl
CCL	$-CF_3$	-H	*-iso*-propyl
CCM	$-CHF_2$	-Cl	-H
CCN	$-CHF_2$	-Br	-H
CCO	$-CHF_2$	-F	-H
CCP	$-CHF_2$	$-CH_3$	-H
CCQ	$-CHF_2$	$-CF_3$	-H
CCR	$-CHF_2$	$-OCH_3$	-H

CCS	$-CHF_2$	$-OCH_2CH_3$	-H
CCT	$-CHF_2$	$-OCF_3$	-H
CCU	$-CHF_2$	-*tert*-butyl	-H
CCV	$-CHF_2$	-*iso*-propyl	-H
CCW	$-CHF_2$	$-CH_3$	$-CH_3$
CCX	$-CHF_2$	-H	-H
CCY	$-CHF_2$	-H	-Cl
CCZ	$-CHF_2$	-H	-Br
CDA	$-CHF_2$	-H	-F
CDB	$-CHF_2$	-H	$-CH_3$
CDC	$-CHF_2$	-H	$-CF_3$
CDD	$-CHF_2$	-H	$-OCH_3$
CDE	$-CHF_2$	-H	$-OCH_2CH_3$
CDF	$-CHF_2$	-H	$-OCF_3$
CDG	$-CHF_2$	-H	-*tert*-butyl
CDH	$-CHF_2$	-H	-*iso*-propyl
CDI	-OH	-Cl	-H
CDJ	-OH	-Br	-H
CDK	-OH	-F	-H
CDL	-OH	$-CH_3$	-H
CDM	-OH	$-CF_3$	-H
CDN	-OH	$-OCH_3$	-H
CDO	-OH	$-OCH_2CH_3$	-H
CDP	-OH	$-OCF_3$	-H
CDQ	-OH	-*tert*-butyl	-H
CDR	-OH	-*iso*-propyl	-H
CDS	-OH	$-CH_3$	$-CH_3$
CDT	-OH	-H	-H
CDU	-OH	-H	-Cl
CDV	-OH	-H	-Br
CDW	-OH	-H	-F
CDX	-OH	-H	$-CH_3$
CDY	-OH	-H	$-CF_3$
CDZ	-OH	-H	$-OCH_3$
CEA	-OH	-H	$-OCH_2CH_3$
CEB	-OH	-H	$-OCF_3$
CEC	-OH	-H	-*tert*-butyl
CED	-OH	-H	-*iso*-propyl
CEE	$-NO_2$	-Cl	-H
CEF	$-NO_2$	-Br	-H
CEG	$-NO_2$	-F	-H
CEH	$-NO_2$	$-CH_3$	-H
CEI	$-NO_2$	$-CF_3$	-H
CEJ	$-NO_2$	$-OCH_3$	-H
CEK	$-NO_2$	$-OCH_2CH_3$	-H
CEL	$-NO_2$	$-OCF_3$	-H
CEM	$-NO_2$	-*tert*-butyl	-H
CEN	$-NO_2$	-*iso*-propyl	-H

CEO	$-NO_2$	$-CH_3$	$-CH_3$
CEP	$-NO_2$	-H	-H
CEQ	$-NO_2$	-H	-Cl
CER	$-NO_2$	-H	-Br
CES	$-NO_2$	-H	-F
CET	$-NO_2$	-H	$-CH_3$
CEU	$-NO_2$	-H	$-CF_3$
CEV	$-NO_2$	-H	$-OCH_3$
CEW	$-NO_2$	-H	$-OCH_2CH_3$
CEX	$-NO_2$	-H	$-OCF_3$
CEY	$-NO_2$	-H	-*tert*-butyl
CEZ	$-NO_2$	-H	-*iso*-propyl
CFA	-CN	-Br	-H
CFB	-CN	-Cl	-H
CFC	-CN	-F	-H
CFD	-CN	$-CH_3$	-H
CFE	-CN	$-CF_3$	-H
CFF	-CN	$-OCH_3$	-H
CFG	-CN	$-OCH_2CH_3$	-H
CFH	-CN	$-OCF_3$	-H
CFI	-CN	-*tert*-butyl	-H
CFJ	-CN	-*iso*-propyl	-H
CFK	-CN	$-CH_3$	$-CH_3$
CFL	-CN	-H	-H
CFM	-CN	-H	-Cl
CFN	-CN	-H	-Br
CFO	-CN	-H	-F
CFP	-CN	-H	$-CH_3$
CFQ	-CN	-H	$-CF_3$
CFR	-CN	-H	$-OCH_3$
CFS	-CN	-H	$-OCH_2CH_3$
CFT	-CN	-H	$-OCF_3$
CFU	-CN	-H	-*tert*-butyl
CFV	-CN	-H	-*iso*-propyl
CFW	-Br	-Br	-H
CFX	-Br	-Cl	-H
CFY	-Br	-F	-H
CFZ	-Br	$-CH_3$	-H
CGA	-Br	$-CF_3$	-H
CGB	-Br	$-OCH_3$	-H
CGC	-Br	$-OCH_2CH_3$	-H
CGD	-Br	$-OCF_3$	-H
CGE	-Br	-*tert*-butyl	-H
CGF	-Br	-*iso*-propyl	-H
CGG	-Br	$-CH_3$	$-CH_3$
CGH	-Br	-H	-H
CGI	-Br	-H	-Cl
CGJ	-Br	-H	-Br

CGK	-Br	-H	-F
CGL	-Br	-H	$-CH_3$
CGM	-Br	-H	$-CF_3$
CGN	-Br	-H	$-OCH_3$
CGO	-Br	-H	$-OCH_2CH_3$
CGP	-Br	-H	$-OCF_3$
CGQ	-Br	-H	-*tert*-butyl
CGR	-Br	-H	-*iso*-propyl
CGS	-I	-Cl	-H
CGT	-I	-Br	-H
CGU	-I	-F	-H
CGV	-I	$-CH_3$	-H
CGW	-I	$-CF_3$	-H
CGX	-I	$-OCH_3$	-H
CGY	-I	$-OCH_2CH_3$	-H
CGZ	-I	$-OCF_3$	-H
CHA	-I	-*tert*-butyl	-H
CHB	-I	-*iso*-propyl	-H
CHC	-I	$-CH_3$	$-CH_3$
CHD	-I	-H	-H
CHE	-I	-H	-Cl
CHF	-I	-H	-Br
CHG	-I	-H	-F
CHH	-I	-H	$-CH_3$
CHI	-I	-*H*	$-CF_3$
CHJ	-I	-H	$-OCH_3$
CHK	-I	-H	$-OCH_2CH_3$
CHL	-I	-H	$-OCF_3$
CHM	-I	-H	-*tert*-butyl
CHN	-I	-H	-*iso*-propyl

Table 11



(Ib)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
CHO	-Cl	-Cl	-H
CHP	-Cl	-Br	-H
CHQ	-Cl	-F	-H
CHR	-Cl	$-CH_3$	-H
CHS	-Cl	$-CF_3$	-H
CHT	-Cl	$-OCH_3$	-H
CHU	-Cl	$-OCH_2CH_3$	-H
CHV	-Cl	$-OCF_3$	-H
CHW	-Cl	-*tert*-butyl	-H
CHX	-Cl	-*iso*-propyl	-H
CHY	-Cl	$-CH_3$	$-CH_3$
CHZ	-Cl	-H	-H
CIA	-Cl	-H	$-CH_3$
CIB	-Cl	-H	$-CF_3$
CIC	-Cl	-H	$-OCH_3$
CID	-Cl	-H	$-OCH_2CH_3$
CIE	-Cl	-H	$-OCF_3$
CIF	-Cl	-H	-*tert*-butyl
CIG	-Cl	-H	-*iso*-propyl
CIH	-Cl	-H	$-OCF_3$
CII	-Cl	-H	-*tert*-butyl
CIJ	-Cl	-H	-*iso*-propyl
CIK	$-CH_3$	-Cl	-H
CIL	$-CH_3$	-Br	-H

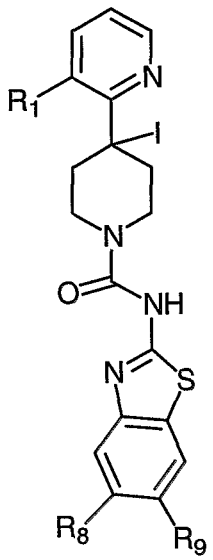
CIM	$-CH_3$	-F	-H
CIN	$-CH_3$	$-CH_3$	-H
CIO	$-CH_3$	$-CF_3$	-H
CIP	$-CH_3$	$-OCH_3$	-H
CIQ	$-CH_3$	$-OCH_2CH_3$	-H
CIR	$-CH_3$	$-OCF_3$	-H
CIS	$-CH_3$	*-tert*-butyl	-H
CIT	$-CH_3$	*-iso*-propyl	-H
CIU	$-CH_3$	$-CH_3$	$-CH_3$
CIV	$-CH_3$	-H	-H
CIW	$-CH_3$	-H	-Cl
CIX	$-CH_3$	-H	-Br
CIY	$-CH_3$	-H	-F
CIZ	$-CH_3$	-H	$-CH_3$
CJA	$-CH_3$	-H	$-CF_3$
CJB	$-CH_3$	-H	$-OCH_3$
CJC	$-CH_3$	-H	$-OCH_2CH_3$
CJD	$-CH_3$	-H	$-OCF_3$
CJE	$-CH_3$	-H	*-tert*-butyl
CJF	$-CH_3$	-H	*-iso*-propyl
CJG	$-CF_3$	-Cl	-H
CJH	$-CF_3$	-Br	-H
CJI	$-CF_3$	-F	-H
CJJ	$-CF_3$	$-CH_3$	-H
CJK	$-CF_3$	$-CF_3$	-H
CJL	$-CF_3$	$-OCH_3$	-H
CJM	$-CF_3$	$-OCH_2CH_3$	-H
CJN	$-CF_3$	$-OCF_3$	-H
CJO	$-CF_3$	*-tert*-butyl	-H
CJP	$-CF_3$	*-iso*-propyl	-H
CJQ	$-CF_3$	$-CH_3$	$-CH_3$
CJR	$-CF_3$	-H	-H
CJS	$-CF_3$	-H	-Cl
CJT	$-CF_3$	-H	-Br
CJU	$-CF_3$	-H	-F
CJV	$-CF_3$	-H	$-CH_3$
CJW	$-CF_3$	-H	$-CF_3$
CJX	$-CF_3$	-H	$-OCH_3$
CJY	$-CF_3$	-H	$-OCH_2CH_3$
CJZ	$-CF_3$	-H	$-OCF_3$
CKA	$-CF_3$	-H	*-tert*-butyl
CKB	$-CF_3$	-H	*-iso*-propyl
CKC	$-CHF_2$	-Cl	-H
CKD	$-CHF_2$	-Br	-H
CKE	$-CHF_2$	-F	-H
CKF	$-CHF_2$	$-CH_3$	-H
CKG	$-CHF_2$	$-CF_3$	-H
CKH	$-CHF_2$	$-OCH_3$	-H

CKI	$-CHF_2$	$-OCH_2CH_3$	-H
CKJ	$-CHF_2$	$-OCF_3$	-H
CKK	$-CHF_2$	-*tert*-butyl	-H
CKL	$-CHF_2$	-*iso*-propyl	-H
CKM	$-CHF_2$	$-CH_3$	$-CH_3$
CKN	$-CHF_2$	-H	-H
CKO	$-CHF_2$	-H	-Cl
CKP	$-CHF_2$	-H	-Br
CKQ	$-CHF_2$	-H	-F
CKR	$-CHF_2$	-H	$-CH_3$
CKS	$-CHF_2$	-H	$-CF_3$
CKT	$-CHF_2$	-H	$-OCH_3$
CKU	$-CHF_2$	-H	$-OCH_2CH_3$
CKV	$-CHF_2$	-H	$-OCF_3$
CKW	$-CHF_2$	-H	-*tert*-butyl
CKX	$-CHF_2$	-H	-*iso*-propyl
CKY	-OH	-Cl	-H
CKZ	-OH	-Br	-H
CLA	-OH	-F	-H
CLB	-OH	$-CH_3$	-H
CLC	-OH	$-CF_3$	-H
CLD	-OH	$-OCH_3$	-H
CLE	-OH	$-OCH_2CH_3$	-H
CLF	-OH	$-OCF_3$	-H
CLG	-OH	-*tert*-butyl	-H
CLH	-OH	-*iso*-propyl	-H
CLI	-OH	$-CH_3$	$-CH_3$
CLJ	-OH	-H	-H
CLK	-OH	-H	-Cl
CLL	-OH	-H	-Br
CLM	-OH	-H	-F
CLN	-OH	-H	$-CH_3$
CLO	-OH	-H	$-CF_3$
CLP	-OH	-H	$-OCH_3$
CLQ	-OH	-H	$-OCH_2CH_3$
CLR	-OH	-H	$-OCF_3$
CLS	-OH	-H	-*tert*-butyl
CLT	-OH	-H	-*iso*-propyl
CLU	$-NO_2$	-Cl	-H
CLV	$-NO_2$	-Br	-H
CLW	$-NO_2$	-F	-H
CLX	$-NO_2$	$-CH_3$	-H
CLY	$-NO_2$	$-CF_3$	-H
CLZ	$-NO_2$	$-OCH_3$	-H
CMA	$-NO_2$	$-OCH_2CH_3$	-H
CMB	$-NO_2$	$-OCF_3$	-H
CMC	$-NO_2$	-*tert*-butyl	-H
CMD	$-NO_2$	-*iso*-propyl	-H

CME	$-NO_2$	$-CH_3$	$-CH_3$
CMF	$-NO_2$	-H	-H
CMG	$-NO_2$	-H	-Cl
CMH	$-NO_2$	-H	-Br
CMI	$-NO_2$	-H	-F
CMJ	$-NO_2$	-H	$-CH_3$
CMK	$-NO_2$	-H	$-CF_3$
CML	$-NO_2$	-H	$-OCH_3$
CMM	$-NO_2$	-H	$-OCH_2CH_3$
CMN	$-NO_2$	-H	$-OCF_3$
CMO	$-NO_2$	-H	*-tert*-butyl
CMP	$-NO_2$	-H	*-iso*-propyl
CMQ	-CN	-Br	-H
CMR	-CN	-Cl	-H
CMS	-CN	-F	-H
CMT	-CN	$-CH_3$	-H
CMU	-CN	$-CF_3$	-H
CMV	-CN	$-OCH_3$	-H
CMW	-CN	$-OCH_2CH_3$	-H
CMX	-CN	$-OCF_3$	-H
CMY	-CN	*-tert*-butyl	-H
CMZ	-CN	*-iso*-propyl	-H
CNA	-CN	$-CH_3$	$-CH_3$
CNB	-CN	-H	-H
CNC	-CN	-H	-Cl
CND	-CN	-H	-Br
CNE	-CN	-H	-F
CNF	-CN	-H	$-CH_3$
CNG	-CN	-H	$-CF_3$
CNH	-CN	-H	$-OCH_3$
CNI	-CN	-H	$-OCH_2CH_3$
CNJ	-CN	-H	$-OCF_3$
CNK	-CN	-H	*-tert*-butyl
CNL	-CN	-H	*-iso*-propyl
CNM	-Br	-Br	-H
CNN	-Br	-Cl	-H
CNO	-Br	-F	-H
CNP	-Br	$-CH_3$	-H
CNQ	-Br	$-CF_3$	-H
CNR	-Br	$-OCH_3$	-H
CNS	-Br	$-OCH_2CH_3$	-H
CNT	-Br	$-OCF_3$	-H
CNU	-Br	*-tert*-butyl	-H
CNV	-Br	*-iso*-propyl	-H
CNW	-Br	$-CH_3$	$-CH_3$
CNX	-Br	-H	-H
CNY	-Br	-H	-Cl
CNZ	-Br	-H	-Br

COA	-Br	-H	-F
COB	-Br	-H	$-CH_3$
COC	-Br	-H	$-CF_3$
COD	-Br	-H	$-OCH_3$
COE	-Br	-H	$-OCH_2CH_3$
COF	-Br	-H	$-OCF_3$
COG	-Br	-H	*-tert*-butyl
COH	-Br	-H	*-iso*-propyl
COI	-I	-Cl	-H
COJ	-I	-Br	-H
COK	-I	-F	-H
COL	-I	$-CH_3$	-H
COM	-I	$-CF_3$	-H
CON	-I	$-OCH_3$	-H
COO	-I	$-OCH_2CH_3$	-H
COP	-I	$-OCF_3$	-H
COQ	-I	*-tert*-butyl	-H
COR	-I	*-iso*-propyl	-H
COS	-I	$-CH_3$	$-CH_3$
COT	-I	-H	-H
COU	-I	-H	-Cl
COV	-I	-H	-Br
COW	-I	-H	-F
COX	-I	-H	$-CH_3$
COY	-I	-H	$-CF_3$
COZ	-I	-H	$-OCH_3$
CPA	-I	-H	$-OCH_2CH_3$
CPB	-I	-H	$-OCF_3$
CPC	-I	-H	*-tert*-butyl
CPD	-I	-H	*-iso*-propyl

Table 12



(Ic)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
CPE	-Cl	-Cl	-H
CPF	-Cl	-Br	-H
CPG	-Cl	-F	-H
CPH	-Cl	$-CH_3$	-H
CPI	-Cl	$-CF_3$	-H
CPJ	-Cl	$-OCH_3$	-H
CPK	-Cl	$-OCH_2CH_3$	-H
CPL	-Cl	$-OCF_3$	-H
CPM	-Cl	*-tert*-butyl	-H
CPN	-Cl	*-iso*-propyl	-H
CPO	-Cl	$-CH_3$	$-CH_3$
CPP	-Cl	-H	-H
CPQ	-Cl	-H	$-CH_3$
CPR	-Cl	-H	$-CF_3$
CPS	-Cl	-H	$-OCH_3$
CPT	-Cl	-H	$-OCH_2CH_3$
CPU	-Cl	-H	$-OCF_3$
CPV	-Cl	-H	*-tert*-butyl
CPW	-Cl	-H	*-iso*-propyl
CPX	-Cl	-H	$-OCF_3$
CPY	-Cl	-H	*-tert*-butyl
CPZ	-Cl	-H	*-iso*-propyl
CQA	$-CH_3$	-Cl	-H
CQB	$-CH_3$	-Br	-H

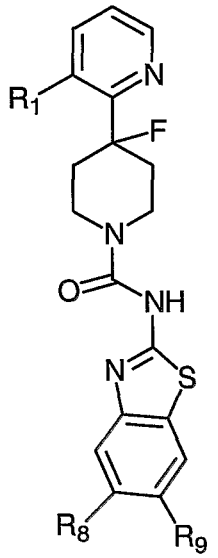
CQC	$-CH_3$	-F	-H
CQD	$-CH_3$	$-CH_3$	-H
CQE	$-CH_3$	$-CF_3$	-H
CQF	$-CH_3$	$-OCH_3$	-H
CQG	$-CH_3$	$-OCH_2CH_3$	-H
CQH	$-CH_3$	$-OCF_3$	-H
CQI	$-CH_3$	*-tert*-butyl	-H
CQJ	$-CH_3$	*-iso*-propyl	-H
CQK	$-CH_3$	$-CH_3$	$-CH_3$
CQL	$-CH_3$	-H	-H
CQM	$-CH_3$	-H	-Cl
CQN	$-CH_3$	-H	-Br
CQO	$-CH_3$	-H	-F
CQP	$-CH_3$	-H	$-CH_3$
CQQ	$-CH_3$	-H	$-CF_3$
CQR	$-CH_3$	-H	$-OCH_3$
CQS	$-CH_3$	-H	$-OCH_2CH_3$
CQT	$-CH_3$	-H	$-OCF_3$
CQU	$-CH_3$	-H	*-tert*-butyl
CQV	$-CH_3$	-H	*-iso*-propyl
CQW	$-CF_3$	-Cl	-H
CQX	$-CF_3$	-Br	-H
CQY	$-CF_3$	-F	-H
CQZ	$-CF_3$	$-CH_3$	-H
CRA	$-CF_3$	$-CF_3$	-H
CRB	$-CF_3$	$-OCH_3$	-H
CRC	$-CF_3$	$-OCH_2CH_3$	-H
CRD	$-CF_3$	$-OCF_3$	-H
CRE	$-CF_3$	*-tert*-butyl	-H
CRF	$-CF_3$	*-iso*-propyl	-H
CRG	$-CF_3$	$-CH_3$	$-CH_3$
CRH	$-CF_3$	-H	-H
CRI	$-CF_3$	-H	-Cl
CRJ	$-CF_3$	-H	-Br
CRK	$-CF_3$	-H	-F
CRL	$-CF_3$	-H	$-CH_3$
CRM	$-CF_3$	-H	$-CF_3$
CRN	$-CF_3$	-H	$-OCH_3$
CRO	$-CF_3$	-H	$-OCH_2CH_3$
CRP	$-CF_3$	-H	$-OCF_3$
CRQ	$-CF_3$	-H	*-tert*-butyl
CRR	$-CF_3$	-H	*-iso*-propyl
CRS	$-CHF_2$	-Cl	-H
CRT	$-CHF_2$	-Br	-H
CRU	$-CHF_2$	-F	-H
CRV	$-CHF_2$	$-CH_3$	-H
CRW	$-CHF_2$	$-CF_3$	-H
CRX	$-CHF_2$	$-OCH_3$	-H

CRY	$-CHF_2$	$-OCH_2CH_3$	-H
CRZ	$-CHF_2$	$-OCF_3$	-H
CSA	$-CHF_2$	*-tert*-butyl	-H
CSB	$-CHF_2$	*-iso*-propyl	-H
CSC	$-CHF_2$	$-CH_3$	$-CH_3$
CSD	$-CHF_2$	-H	-H
CSE	$-CHF_2$	-H	-Cl
CSF	$-CHF_2$	-H	-Br
CSG	$-CHF_2$	-H	-F
CSH	$-CHF_2$	-H	$-CH_3$
CSI	$-CHF_2$	-H	$-CF_3$
CSJ	$-CHF_2$	-H	$-OCH_3$
CSK	$-CHF_2$	-H	$-OCH_2CH_3$
CSL	$-CHF_2$	-H	$-OCF_3$
CSM	$-CHF_2$	-H	*-tert*-butyl
CSN	$-CHF_2$	-H	*-iso*-propyl
CSO	-OH	-Cl	-H
CSP	-OH	-Br	-H
CSQ	-OH	-F	-H
CSR	-OH	$-CH_3$	-H
CSS	-OH	$-CF_3$	-H
CST	-OH	$-OCH_3$	-H
CSU	-OH	$-OCH_2CH_3$	-H
CSV	-OH	$-OCF_3$	-H
CSW	-OH	*-tert*-butyl	-H
CSX	-OH	*-iso*-propyl	-H
CSY	-OH	$-CH_3$	$-CH_3$
CSZ	-OH	-H	-H
CTA	-OH	-H	-Cl
CTB	-OH	-H	-Br
CTC	-OH	-H	-F
CTD	-OH	-H	$-CH_3$
CTE	-OH	-H	$-CF_3$
CTF	-OH	-H	$-OCH_3$
CTG	-OH	-H	$-OCH_2CH_3$
CTH	-OH	-H	$-OCF_3$
CTI	-OH	-H	*-tert*-butyl
CTJ	-OH	-H	*-iso*-propyl
CTK	$-NO_2$	-Cl	-H
CTL	$-NO_2$	-Br	-H
CTM	$-NO_2$	-F	-H
CTN	$-NO_2$	$-CH_3$	-H
CTO	$-NO_2$	$-CF_3$	-H
CTP	$-NO_2$	$-OCH_3$	-H
CTQ	$-NO_2$	$-OCH_2CH_3$	-H
CTR	$-NO_2$	$-OCF_3$	-H
CTS	$-NO_2$	*-tert*-butyl	-H
CTT	$-NO_2$	*-iso*-propyl	-H

CTU	$-NO_2$	$-CH_3$	$-CH_3$
CTV	$-NO_2$	-H	-H
CTW	$-NO_2$	-H	-Cl
CTX	$-NO_2$	-H	-Br
CTY	$-NO_2$	-H	-F
CTZ	$-NO_2$	-H	$-CH_3$
CUA	$-NO_2$	-H	$-CF_3$
CUB	$-NO_2$	-H	$-OCH_3$
CUC	$-NO_2$	-H	$-OCH_2CH_3$
CUD	$-NO_2$	-H	$-OCF_3$
CUE	$-NO_2$	-H	*-tert*-butyl
CUF	$-NO_2$	-H	*-iso*-propyl
CUG	-CN	-Br	-H
CUH	-CN	-Cl	-H
CUI	-CN	-F	-H
CUJ	-CN	$-CH_3$	-H
CUK	-CN	$-CF_3$	-H
CUL	-CN	$-OCH_3$	-H
CUM	-CN	$-OCH_2CH_3$	-H
CUN	-CN	$-OCF_3$	-H
CUO	-CN	*-tert*-butyl	-H
CUP	-CN	*-iso*-propyl	-H
CUQ	-CN	$-CH_3$	$-CH_3$
CUR	-CN	-H	-H
CUS	-CN	-H	-Cl
CUT	-CN	-H	-Br
CUU	-CN	-H	-F
CUV	-CN	-H	$-CH_3$
CUW	-CN	-H	$-CF_3$
CUX	-CN	-H	$-OCH_3$
CUY	-CN	-H	$-OCH_2CH_3$
CUZ	-CN	-H	$-OCF_3$
CVA	-CN	-H	*-tert*-butyl
CVB	-CN	-H	*-iso*-propyl
CVC	-Br	-Br	-H
CVD	-Br	-Cl	-H
CVE	-Br	-F	-H
CVF	-Br	$-CH_3$	-H
CVG	-Br	$-CF_3$	-H
CVH	-Br	$-OCH_3$	-H
CVI	-Br	$-OCH_2CH_3$	-H
CVJ	-Br	$-OCF_3$	-H
CVK	-Br	*-tert*-butyl	-H
CVL	-Br	*-iso*-propyl	-H
CVM	-Br	$-CH_3$	$-CH_3$
CVN	-Br	-H	-H
CVO	-Br	-H	-Cl
CVP	-Br	-H	-Br

CVQ	-Br	-H	-F
CVR	-Br	-H	$-CH_3$
CVS	-Br	-H	$-CF_3$
CVT	-Br	-H	$-OCH_3$
CVU	-Br	-H	$-OCH_2CH_3$
CVV	-Br	-H	$-OCF_3$
CVW	-Br	-H	*-tert*-butyl
CVX	-Br	-H	*-iso*-propyl
CVY	-I	-Cl	-H
CVZ	-I	-Br	-H
CWA	-I	-F	-H
CWB	-I	$-CH_3$	-H
CWC	-I	$-CF_3$	-H
CWD	-I	$-OCH_3$	-H
CWE	-I	$-OCH_2CH_3$	-H
CWF	-I	$-OCF_3$	-H
CWG	-I	*-tert*-butyl	-H
CWH	-I	*-iso*-propyl	-H
CWI	-I	$-CH_3$	$-CH_3$
CWJ	-I	-H	-H
CWK	-I	-H	-Cl
CWL	-I	-H	-Br
CWM	-I	-H	-F
CWN	-I	-H	$-CH_3$
CWO	-I	-H	$-CF_3$
CWP	-I	-H	$-OCH_3$
CWQ	-I	-H	$-OCH_2CH_3$
CWR	-I	-H	$-OCF_3$
CWS	-I	-H	*-tert*-butyl
CWT	-I	-H	*-iso*-propyl

Table 13



(Id)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
CWU	-Cl	-Cl	-H
CWV	-Cl	-Br	-H
CWW	-Cl	-F	-H
CWX	-Cl	$-CH_3$	-H
CWY	-Cl	$-CF_3$	-H
CWZ	-Cl	$-OCH_3$	-H
CXA	-Cl	$-OCH_2CH_3$	-H
CXB	-Cl	$-OCF_3$	-H
CXC	-Cl	*-tert*-butyl	-H
CXD	-Cl	*-iso*-propyl	-H
CXE	-Cl	$-CH_3$	$-CH_3$
CXF	-Cl	-H	-H
CXG	-Cl	-H	$-CH_3$
CXH	-Cl	-H	$-CF_3$
CXI	-Cl	-H	$-OCH_3$
CXJ	-Cl	-H	$-OCH_2CH_3$
CXK	-Cl	-H	$-OCF_3$
CXL	-Cl	-H	*-tert*-butyl
CXM	-Cl	-H	*-iso*-propyl
CXN	-Cl	-H	$-OCF_3$
CXO	-Cl	-H	*-tert*-butyl
CXP	-Cl	-H	*-iso*-propyl
CXQ	$-CH_3$	-Cl	-H
CXR	$-CH_3$	-Br	-H

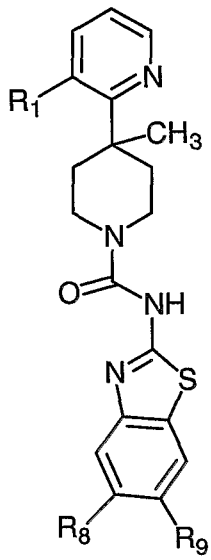
CXS	$-CH_3$	-F	-H
CXT	$-CH_3$	$-CH_3$	-H
CXU	$-CH_3$	$-CF_3$	-H
CXV	$-CH_3$	$-OCH_3$	-H
CXW	$-CH_3$	$-OCH_2CH_3$	-H
CXX	$-CH_3$	$-OCF_3$	-H
CXY	$-CH_3$	*-tert*-butyl	-H
CXZ	$-CH_3$	*-iso*-propyl	-H
CYA	$-CH_3$	$-CH_3$	$-CH_3$
CYB	$-CH_3$	-H	-H
CYC	$-CH_3$	-H	-Cl
CYD	$-CH_3$	-H	-Br
CYE	$-CH_3$	-H	-F
CYF	$-CH_3$	-H	$-CH_3$
CYG	$-CH_3$	-H	$-CF_3$
CYH	$-CH_3$	-H	$-OCH_3$
CYI	$-CH_3$	-H	$-OCH_2CH_3$
CYJ	$-CH_3$	-H	$-OCF_3$
CYK	$-CH_3$	-H	*-tert*-butyl
CYL	$-CH_3$	-H	*-iso*-propyl
CYM	$-CF_3$	-Cl	-H
CYN	$-CF_3$	-Br	-H
CYO	$-CF_3$	-F	-H
CYP	$-CF_3$	$-CH_3$	-H
CYQ	$-CF_3$	$-CF_3$	-H
CYR	$-CF_3$	$-OCH_3$	-H
CYS	$-CF_3$	$-OCH_2CH_3$	-H
CYT	$-CF_3$	$-OCF_3$	-H
CYU	$-CF_3$	*-tert*-butyl	-H
CYV	$-CF_3$	*-iso*-propyl	-H
CYW	$-CF_3$	$-CH_3$	$-CH_3$
CYX	$-CF_3$	-H	-H
CYY	$-CF_3$	-H	-Cl
CYZ	$-CF_3$	-H	-Br
CZA	$-CF_3$	-H	-F
CZB	$-CF_3$	-H	$-CH_3$
CZC	$-CF_3$	-H	$-CF_3$
CZD	$-CF_3$	-H	$-OCH_3$
CZE	$-CF_3$	-H	$-OCH_2CH_3$
CZF	$-CF_3$	-H	$-OCF_3$
CZG	$-CF_3$	-H	*-tert*-butyl
CZH	$-CF_3$	-H	*-iso*-propyl
CZI	$-CHF_2$	-Cl	-H
CZJ	$-CHF_2$	-Br	-H
CZK	$-CHF_2$	-F	-H
CZL	$-CHF_2$	$-CH_3$	-H
CZM	$-CHF_2$	$-CF_3$	-H
CZN	$-CHF_2$	$-OCH_3$	-H

CZO	$-CHF_2$	$-OCH_2CH_3$	-H
CZP	$-CHF_2$	$-OCF_3$	-H
CZQ	$-CHF_2$	*-tert*-butyl	-H
CZR	$-CHF_2$	*-iso*-propyl	-H
CZS	$-CHF_2$	$-CH_3$	$-CH_3$
CZT	$-CHF_2$	-H	-H
CZU	$-CHF_2$	-H	-Cl
CZV	$-CHF_2$	-H	-Br
CZW	$-CHF_2$	-H	-F
CZX	$-CHF_2$	-H	$-CH_3$
CZY	$-CHF_2$	-H	$-CF_3$
CZZ	$-CHF_2$	-H	$-OCH_3$
DAA	$-CHF_2$	-H	$-OCH_2CH_3$
DAB	$-CHF_2$	-H	$-OCF_3$
DAC	$-CHF_2$	-H	*-tert*-butyl
DAD	$-CHF_2$	-H	*-iso*-propyl
DAE	-OH	-Cl	-H
DAF	-OH	-Br	-H
DAG	-OH	-F	-H
DAH	-OH	$-CH_3$	-H
DAI	-OH	$-CF_3$	-H
DAJ	-OH	$-OCH_3$	-H
DAK	-OH	$-OCH_2CH_3$	-H
DAL	-OH	$-OCF_3$	-H
DAM	-OH	*-tert*-butyl	-H
DAN	-OH	*-iso*-propyl	-H
DAO	-OH	$-CH_3$	$-CH_3$
DAP	-OH	-H	-H
DAQ	-OH	-H	-Cl
DAR	-OH	-H	-Br
DAS	-OH	-H	-F
DAT	-OH	-H	$-CH_3$
DAU	-OH	-H	$-CF_3$
DAV	-OH	-H	$-OCH_3$
DAW	-OH	-H	$-OCH_2CH_3$
DAX	-OH	-H	$-OCF_3$
DAY	-OH	-H	*-tert*-butyl
DAZ	-OH	-H	*-iso*-propyl
DBA	$-NO_2$	-Cl	-H
DBB	$-NO_2$	-Br	-H
DBC	$-NO_2$	-F	-H
DBD	$-NO_2$	$-CH_3$	-H
DBE	$-NO_2$	$-CF_3$	-H
DBF	$-NO_2$	$-OCH_3$	-H
DBG	$-NO_2$	$-OCH_2CH_3$	-H
DBH	$-NO_2$	$-OCF_3$	-H
DBI	$-NO_2$	*-tert*-butyl	-H
DBJ	$-NO_2$	*-iso*-propyl	-H

DBK	$-NO_2$	$-CH_3$	$-CH_3$
DBL	$-NO_2$	-H	-H
DBM	$-NO_2$	-H	-Cl
DBN	$-NO_2$	-H	-Br
DBO	$-NO_2$	-H	-F
DBP	$-NO_2$	-H	$-CH_3$
DBQ	$-NO_2$	-H	$-CF_3$
DBR	$-NO_2$	-H	$-OCH_3$
DBS	$-NO_2$	-H	$-OCH_2CH_3$
DBT	$-NO_2$	-H	$-OCF_3$
DBU	$-NO_2$	-H	-*tert*-butyl
DBV	$-NO_2$	-H	-*iso*-propyl
DBW	-CN	-Br	-H
DBX	-CN	-Cl	-H
DBY	-CN	-F	-H
DBZ	-CN	$-CH_3$	-H
DCA	-CN	$-CF_3$	-H
DCB	-CN	$-OCH_3$	-H
DCC	-CN	$-OCH_2CH_3$	-H
DCD	-CN	$-OCF_3$	-H
DCE	-CN	-*tert*-butyl	-H
DCF	-CN	-*iso*-propyl	-H
DCG	-CN	$-CH_3$	$-CH_3$
DCH	-CN	-H	-H
DCI	-CN	-H	-Cl
DCJ	-CN	-H	-Br
DCK	-CN	-H	-F
DCL	-CN	-H	$-CH_3$
DCM	-CN	-H	$-CF_3$
DCN	-CN	-H	$-OCH_3$
DCO	-CN	-H	$-OCH_2CH_3$
DCP	-CN	-H	$-OCF_3$
DCQ	-CN	-H	-*tert*-butyl
DCR	-CN	-H	-*iso*-propyl
DCS	-Br	-Br	-H
DCT	-Br	-Cl	-H
DCU	-Br	-F	-H
DCV	-Br	$-CH_3$	-H
DCW	-Br	$-CF_3$	-H
DCX	-Br	$-OCH_3$	-H
DCY	-Br	$-OCH_2CH_3$	-H
DCZ	-Br	$-OCF_3$	-H
DDA	-Br	-*tert*-butyl	-H
DDB	-Br	-*iso*-propyl	-H
DDC	-Br	$-CH_3$	$-CH_3$
DDD	-Br	-H	-H
DDE	-Br	-H	-Cl
DDF	-Br	-H	-Br

DDG	-Br	-H	-F
DDH	-Br	-H	$-CH_3$
DDI	-Br	-H	$-CF_3$
DDJ	-Br	-H	$-OCH_3$
DDK	-Br	-H	$-OCH_2CH_3$
DDL	-Br	-H	$-OCF_3$
DDM	-Br	-H	-*tert*-butyl
DDN	-Br	-H	-*iso*-propyl
DDO	-I	-Cl	-H
DDP	-I	-Br	-H
DDQ	-I	-F	-H
DDR	-I	$-CH_3$	-H
DDS	-I	$-CF_3$	-H
DDT	-I	$-OCH_3$	-H
DDU	-I	$-OCH_2CH_3$	-H
DDV	-I	$-OCF_3$	-H
DDW	-I	-*tert*-butyl	-H
DDX	-I	-*iso*-propyl	-H
DDY	-I	$-CH_3$	$-CH_3$
DDZ	-I	-H	-H
DEA	-I	-H	-Cl
DEB	-I	-H	-Br
DEC	-I	-H	-F
DED	-I	-H	$-CH_3$
DEE	-I	-H	$-CF_3$
DEF	-I	-H	$-OCH_3$
DEG	-I	-H	$-OCH_2CH_3$
DEH	-I	-H	$-OCF_3$
DEI	-I	-H	-*tert*-butyl
DEJ	-I	-H	-*iso*-propyl

Table 14



(Ie)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
DEK	-Cl	-Cl	-H
DEL	-Cl	-Br	-H
DEM	-Cl	-F	-H
DEN	-Cl	$-CH_3$	-H
DEO	-Cl	$-CF_3$	-H
DEP	-Cl	$-OCH_3$	-H
DEQ	-Cl	$-OCH_2CH_3$	-H
DER	-Cl	$-OCF_3$	-H
DES	-Cl	*-tert*-butyl	-H
DET	-Cl	*-iso*-propyl	-H
DEU	-Cl	$-CH_3$	$-CH_3$
DEV	-Cl	-H	-H
DEW	-Cl	-H	$-CH_3$
DEX	-Cl	-H	$-CF_3$
DEY	-Cl	-H	$-OCH_3$
DEZ	-Cl	-H	$-OCH_2CH_3$
DFA	-Cl	-H	$-OCF_3$
DFB	-Cl	-H	*-tert*-butyl
DFC	-Cl	-H	*-iso*-propyl
DFD	-Cl	-H	$-OCF_3$
DFE	-Cl	-H	*-tert*-butyl
DFF	-Cl	-H	*-iso*-propyl
DFG	$-CH_3$	-Cl	-H
DFH	$-CH_3$	-Br	-H

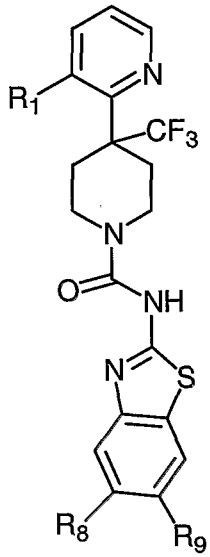
DFI	$-CH_3$	-F	-H
DFJ	$-CH_3$	$-CH_3$	-H
DFK	$-CH_3$	$-CF_3$	-H
DFL	$-CH_3$	$-OCH_3$	-H
DFM	$-CH_3$	$-OCH_2CH_3$	-H
DFN	$-CH_3$	$-OCF_3$	-H
DFO	$-CH_3$	*-tert*-butyl	-H
DFP	$-CH_3$	*-iso*-propyl	-H
DFQ	$-CH_3$	$-CH_3$	$-CH_3$
DFR	$-CH_3$	-H	-H
DFS	$-CH_3$	-H	-Cl
DFT	$-CH_3$	-H	-Br
DFU	$-CH_3$	-H	-F
DFV	$-CH_3$	-H	$-CH_3$
DFW	$-CH_3$	-H	$-CF_3$
DFX	$-CH_3$	-H	$-OCH_3$
DFY	$-CH_3$	-H	$-OCH_2CH_3$
DFZ	$-CH_3$	-H	$-OCF_3$
DGA	$-CH_3$	-H	*-tert*-butyl
DGB	$-CH_3$	-H	*-iso*-propyl
DGC	$-CF_3$	-Cl	-H
DGD	$-CF_3$	-Br	-H
DGE	$-CF_3$	-F	-H
DGF	$-CF_3$	$-CH_3$	-H
DGG	$-CF_3$	$-CF_3$	-H
DGH	$-CF_3$	$-OCH_3$	-H
DGI	$-CF_3$	$-OCH_2CH_3$	-H
DGJ	$-CF_3$	$-OCF_3$	-H
DGK	$-CF_3$	*-tert*-butyl	-H
DGL	$-CF_3$	*-iso*-propyl	-H
DGM	$-CF_3$	$-CH_3$	$-CH_3$
DGN	$-CF_3$	-H	-H
DGO	$-CF_3$	-H	-Cl
DGP	$-CF_3$	-H	-Br
DGQ	$-CF_3$	-H	-F
DGR	$-CF_3$	-H	$-CH_3$
DGS	$-CF_3$	-H	$-CF_3$
DGT	$-CF_3$	-H	$-OCH_3$
DGU	$-CF_3$	-H	$-OCH_2CH_3$
DGV	$-CF_3$	-H	$-OCF_3$
DGW	$-CF_3$	-H	*-tert*-butyl
DGX	$-CF_3$	-H	*-iso*-propyl
DGY	$-CHF_2$	-Cl	-H
DGZ	$-CHF_2$	-Br	-H
DHA	$-CHF_2$	-F	-H
DHB	$-CHF_2$	$-CH_3$	-H
DHC	$-CHF_2$	$-CF_3$	-H
DHD	$-CHF_2$	$-OCH_3$	-H

DHE	$-CHF_2$	$-OCH_2CH_3$	-H
DHF	$-CHF_2$	$-OCF_3$	-H
DHG	$-CHF_2$	*-tert*-butyl	-H
DHH	$-CHF_2$	*-iso*-propyl	-H
DHI	$-CHF_2$	$-CH_3$	$-CH_3$
DHJ	$-CHF_2$	-H	-H
DHK	$-CHF_2$	-H	-Cl
DHL	$-CHF_2$	-H	-Br
DHM	$-CHF_2$	-H	-F
DHN	$-CHF_2$	-H	$-CH_3$
DHO	$-CHF_2$	-H	$-CF_3$
DHP	$-CHF_2$	-H	$-OCH_3$
DHQ	$-CHF_2$	-H	$-OCH_2CH_3$
DHR	$-CHF_2$	-H	$-OCF_3$
DHS	$-CHF_2$	-H	*-tert*-butyl
DHT	$-CHF_2$	-H	*-iso*-propyl
DHU	-OH	-Cl	-H
DHV	-OH	-Br	-H
DHW	-OH	-F	-H
DHX	-OH	$-CH_3$	-H
DHY	-OH	$-CF_3$	-H
DHZ	-OH	$-OCH_3$	-H
DIA	-OH	$-OCH_2CH_3$	-H
DIB	-OH	$-OCF_3$	-H
DIC	*-OH*	*-tert-butyl*	*-H*
DID	-OH	*-iso*-propyl	-H
DIE	-OH	$-CH_3$	$-CH_3$
DIF	-OH	-H	-H
DIG	-OH	-H	-Cl
DIH	-OH	-H	-Br
DII	-OH	-H	-F
DIJ	-OH	-H	$-CH_3$
DIK	-OH	-H	$-CF_3$
DIL	-OH	-H	$-OCH_3$
DIM	-OH	-H	$-OCH_2CH_3$
DIN	-OH	-H	$-OCF_3$
DIO	-OH	-H	*-tert*-butyl
DIP	-OH	-H	*-iso*-propyl
DIQ	$-NO_2$	-Cl	-H
DIR	$-NO_2$	-Br	-H
DIS	$-NO_2$	-F	-H
DIT	$-NO_2$	$-CH_3$	-H
DIU	$-NO_2$	$-CF_3$	-H
DIV	$-NO_2$	$-OCH_3$	-H
DIW	$-NO_2$	$-OCH_2CH_3$	-H
DIX	$-NO_2$	$-OCF_3$	-H
DIY	$-NO_2$	*-tert*-butyl	-H
DIZ	$-NO_2$	*-iso*-propyl	-H

DJA	$-NO_2$	$-CH_3$	$-CH_3$
DJB	$-NO_2$	-H	-H
DJC	$-NO_2$	-H	-Cl
DJD	$-NO_2$	-H	-Br
DJE	$-NO_2$	-H	-F
DJF	$-NO_2$	-H	$-CH_3$
DJG	$-NO_2$	-H	$-CF_3$
DJH	$-NO_2$	-H	$-OCH_3$
DJI	$-NO_2$	-H	$-OCH_2CH_3$
DJJ	$-NO_2$	-H	$-OCF_3$
DJK	$-NO_2$	-H	-*tert*-butyl
DJL	$-NO_2$	-H	-*iso*-propyl
DJM	-CN	-Br	-H
DJN	-CN	-Cl	-H
DJO	-CN	-F	-H
DJP	-CN	$-CH_3$	-H
DJQ	-CN	$-CF_3$	-H
DJR	-CN	$-OCH_3$	-H
DJS	-CN	$-OCH_2CH_3$	-H
DJT	-CN	$-OCF_3$	-H
DJU	-CN	-*tert*-butyl	-H
DJV	-CN	-*iso*-propyl	-H
DJW	-CN	$-CH_3$	$-CH_3$
DJX	-CN	-H	-H
DJY	-CN	-*H*	-*Cl*
DJZ	-CN	-H	-Br
DKA	-CN	-H	-F
DKB	-CN	-H	$-CH_3$
DKC	-CN	-H	$-CF_3$
DKD	-CN	-H	$-OCH_3$
DKE	-CN	-H	$-OCH_2CH_3$
DKF	-CN	-H	$-OCF_3$
DKG	-CN	-H	-*tert*-butyl
DKH	-CN	-H	-*iso*-propyl
DKI	-Br	-Br	-H
DKJ	-Br	-Cl	-H
DKK	-Br	-F	-H
DKL	-Br	$-CH_3$	-H
DKM	-Br	$-CF_3$	-H
DKN	-Br	$-OCH_3$	-H
DKO	-Br	$-OCH_2CH_3$	-H
DKP	-Br	$-OCF_3$	-H
DKQ	-Br	-*tert*-butyl	-H
DKR	-Br	-*iso*-propyl	-H
DKS	-Br	$-CH_3$	$-CH_3$
DKT	-Br	-H	-H
DKU	-Br	-H	-Cl
DKV	-Br	-H	-Br

DKW	-Br	-H	-F
DKX	-Br	-H	$-CH_3$
DKY	-Br	-H	$-CF_3$
DKZ	-Br	-H	$-OCH_3$
DLA	-Br	-H	$-OCH_2CH_3$
DLB	-Br	-H	$-OCF_3$
DLC	-Br	-H	*-tert*-butyl
DLD	-Br	-H	*-iso*-propyl
DLE	-I	-Cl	-H
DLF	-I	-Br	-H
DLG	-I	-F	-H
DLH	-I	$-CH_3$	-H
DLI	-I	$-CF_3$	-H
DLJ	-I	$-OCH_3$	-H
DLK	-I	$-OCH_2CH_3$	-H
DLL	-I	$-OCF_3$	-H
DLM	-I	*-tert*-butyl	-H
DLN	-I	*-iso*-propyl	-H
DLO	-I	$-CH_3$	$-CH_3$
DLP	-I	-H	-H
DLQ	-I	-H	-Cl
DLR	-I	-H	-Br
DLS	-I	-H	-F
DLT	-I	-H	$-CH_3$
DLU	-I	-H	$-CF_3$
DLV	-I	-H	$-OCH_3$
DLW	-I	-H	$-OCH_2CH_3$
DLX	-I	-H	$-OCF_3$
DLY	-I	-H	*-tert*-butyl
DLZ	-I	-H	*-iso*-propyl

Table 15



(If)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
DMA	-Cl	-Cl	-H
DMB	-Cl	-Br	-H
DMC	-Cl	-F	-H
DMD	-Cl	$-CH_3$	-H
DME	-Cl	$-CF_3$	-H
DMF	-Cl	$-OCH_3$	-H
DMG	-Cl	$-OCH_2CH_3$	-H
DMH	-Cl	$-OCF_3$	-H
DMI	-Cl	-*tert*-butyl	-H
DMJ	-Cl	-*iso*-propyl	-H
DMK	-Cl	$-CH_3$	$-CH_3$
DML	-Cl	-H	-H
DMM	-Cl	-H	$-CH_3$
DMN	-Cl	-H	$-CF_3$
DMO	-Cl	-H	$-OCH_3$
DMP	-Cl	-H	$-OCH_2CH_3$
DMQ	-Cl	-H	$-OCF_3$
DMR	-Cl	-H	-*tert*-butyl
DMS	-Cl	-H	-*iso*-propyl
DMT	-Cl	-H	$-OCF_3$
DMU	-Cl	-H	-*tert*-butyl
DMV	-Cl	-H	-*iso*-propyl
DMW	$-CH_3$	-Cl	-H
DMX	$-CH_3$	-Br	-H

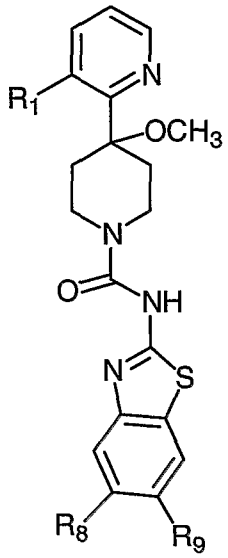
DMY	$-CH_3$	-F	-H
DMZ	$-CH_3$	$-CH_3$	-H
DNA	$-CH_3$	$-CF_3$	-H
DNB	$-CH_3$	$-OCH_3$	-H
DNC	$-CH_3$	$-OCH_2CH_3$	-H
DND	$-CH_3$	$-OCF_3$	-H
DNE	$-CH_3$	*-tert*-butyl	-H
DNF	$-CH_3$	*-iso*-propyl	-H
DNG	$-CH_3$	$-CH_3$	$-CH_3$
DNH	$-CH_3$	-H	-H
DNI	$-CH_3$	-H	-Cl
DNJ	$-CH_3$	-H	-Br
DNK	$-CH_3$	-H	-F
DNL	$-CH_3$	-H	$-CH_3$
DNM	$-CH_3$	-H	$-CF_3$
DNN	$-CH_3$	-H	$-OCH_3$
DNO	$-CH_3$	-H	$-OCH_2CH_3$
DNP	$-CH_3$	-H	$-OCF_3$
DNQ	$-CH_3$	-H	*-tert*-butyl
DNR	$-CH_3$	-H	*-iso*-propyl
DNS	$-CF_3$	-Cl	-H
DNT	$-CF_3$	-Br	-H
DNU	$-CF_3$	-F	-H
DNV	$-CF_3$	$-CH_3$	-H
DNW	$-CF_3$	$-CF_3$	-H
DNX	$-CF_3$	$-OCH_3$	-H
DNY	$-CF_3$	$-OCH_2CH_3$	-H
DNZ	$-CF_3$	$-OCF_3$	-H
DOA	$-CF_3$	*-tert*-butyl	-H
DOB	$-CF_3$	*-iso*-propyl	-H
DOC	$-CF_3$	$-CH_3$	$-CH_3$
DOD	$-CF_3$	-H	-H
DOE	$-CF_3$	-H	-Cl
DOF	$-CF_3$	-H	-Br
DOG	$-CF_3$	-H	-F
DOH	$-CF_3$	-H	$-CH_3$
DOI	$-CF_3$	-H	$-CF_3$
DOJ	$-CF_3$	-H	$-OCH_3$
DOK	$-CF_3$	-H	$-OCH_2CH_3$
DOL	$-CF_3$	-H	$-OCF_3$
DOM	$-CF_3$	-H	*-tert*-butyl
DON	$-CF_3$	-H	*-iso*-propyl
DOO	$-CHF_2$	-Cl	-H
DOP	$-CHF_2$	-Br	-H
DOQ	$-CHF_2$	-F	-H
DOR	$-CHF_2$	$-CH_3$	-H
DOS	$-CHF_2$	$-CF_3$	-H
DOT	$-CHF_2$	$-OCH_3$	-H

DOU	$-CHF_2$	$-OCH_2CH_3$	-H
DOV	$-CHF_2$	$-OCF_3$	-H
DOW	$-CHF_2$	*-tert*-butyl	-H
DOX	$-CHF_2$	*-iso*-propyl	-H
DOY	$-CHF_2$	$-CH_3$	$-CH_3$
DOZ	$-CHF_2$	-H	-H
DPA	$-CHF_2$	-H	-Cl
DPB	$-CHF_2$	-H	-Br
DPC	$-CHF_2$	-H	-F
DPD	$-CHF_2$	-H	$-CH_3$
DPE	$-CHF_2$	-H	$-CF_3$
DPF	$-CHF_2$	-H	$-OCH_3$
DPG	$-CHF_2$	-H	$-OCH_2CH_3$
DPH	$-CHF_2$	-H	$-OCF_3$
DPI	$-CHF_2$	-H	*-tert*-butyl
DPJ	$-CHF_2$	-H	*-iso*-propyl
DPK	-OH	-Cl	-H
DPL	-OH	-Br	-H
DPM	-OH	-F	-H
DPN	-OH	$-CH_3$	-H
DPO	-OH	$-CF_3$	-H
DPP	-OH	$-OCH_3$	-H
DPQ	-OH	$-OCH_2CH_3$	-H
DPR	-OH	$-OCF_3$	-H
DPS	-OH	*-tert*-butyl	-H
DPT	-OH	*-iso*-propyl	-H
DPU	-OH	$-CH_3$	$-CH_3$
DPV	-OH	-H	-H
DPW	-OH	-H	-Cl
DPX	-OH	-H	-Br
DPY	-OH	-H	-F
DPZ	-OH	-H	$-CH_3$
DQA	-OH	-H	$-CF_3$
DQB	-OH	-H	$-OCH_3$
DQC	-OH	-H	$-OCH_2CH_3$
DQD	-OH	-H	$-OCF_3$
DQE	-OH	-H	*-tert*-butyl
DQF	-OH	-H	*-iso*-propyl
DQG	$-NO_2$	-Cl	-H
DQH	$-NO_2$	-Br	-H
DQI	$-NO_2$	-F	-H
DQJ	$-NO_2$	$-CH_3$	-H
DQK	$-NO_2$	$-CF_3$	-H
DQL	$-NO_2$	$-OCH_3$	-H
DQM	$-NO_2$	$-OCH_2CH_3$	-H
DQN	$-NO_2$	$-OCF_3$	-H
DQO	$-NO_2$	*-tert*-butyl	-H
DQP	$-NO_2$	*-iso*-propyl	-H

DQQ	$-NO_2$	$-CH_3$	$-CH_3$
DQR	$-NO_2$	-H	-H
DQS	$-NO_2$	-H	-Cl
DQT	$-NO_2$	-H	-Br
DQU	$-NO_2$	-H	-F
DQV	$-NO_2$	-H	$-CH_3$
DQW	$-NO_2$	-H	$-CF_3$
DQX	$-NO_2$	-H	$-OCH_3$
DQY	$-NO_2$	-H	$-OCH_2CH_3$
DQZ	$-NO_2$	-H	$-OCF_3$
DRA	$-NO_2$	-H	*-tert*-butyl
DRB	$-NO_2$	-H	*-iso*-propyl
DRC	-CN	-Br	-H
DRD	-CN	-Cl	-H
DRE	-CN	-F	-H
DRF	-CN	$-CH_3$	-H
DRG	-CN	$-CF_3$	-H
DRH	-CN	$-OCH_3$	-H
DRI	-CN	$-OCH_2CH_3$	-H
DRJ	-CN	$-OCF_3$	-H
DRK	-CN	*-tert*-butyl	-H
DRL	-CN	*-iso*-propyl	-H
DRM	-CN	$-CH_3$	$-CH_3$
DRN	-CN	-H	-H
DRO	-CN	-H	-Cl
DRP	-CN	-H	-Br
DRQ	-CN	-H	-F
DRR	-CN	-H	$-CH_3$
DRS	-CN	-H	$-CF_3$
DRT	-CN	-H	$-OCH_3$
DRU	-CN	-H	$-OCH_2CH_3$
DRV	-CN	-H	$-OCF_3$
DRW	-CN	-H	*-tert*-butyl
DRX	-CN	-H	*-iso*-propyl
DRY	-Br	-Br	-H
DRZ	-Br	-Cl	-H
DSA	-Br	-F	-H
DSB	-Br	$-CH_3$	-H
DSC	-Br	$-CF_3$	-H
DSD	-Br	$-OCH_3$	-H
DSE	-Br	$-OCH_2CH_3$	-H
DSF	-Br	$-OCF_3$	-H
DSG	-Br	*-tert*-butyl	-H
DSH	-Br	*-iso*-propyl	-H
DSI	-Br	$-CH_3$	$-CH_3$
DSJ	-Br	-H	-H
DSK	-Br	-H	-Cl
DSL	-Br	-H	-Br

DSM	-Br	-H	-F
DSN	-Br	-H	$-CH_3$
DSO	-Br	-H	$-CF_3$
DSP	-Br	-H	$-OCH_3$
DSQ	-Br	-H	$-OCH_2CH_3$
DSR	-Br	-H	$-OCF_3$
DSS	-Br	-H	-*tert*-butyl
DST	-Br	-H	-*iso*-propyl
DSU	-I	-Cl	-H
DSV	-I	-Br	-H
DSW	-I	-F	-H
DSX	-I	$-CH_3$	-H
DSY	-I	$-CF_3$	-H
DSZ	-I	$-OCH_3$	-H
DTA	-I	$-OCH_2CH_3$	-H
DTB	-I	$-OCF_3$	-H
DTC	-I	-*tert*-butyl	-H
DTD	-I	-*iso*-propyl	-H
DTE	-I	$-CH_3$	$-CH_3$
DTF	-I	-H	-H
DTG	-I	-H	-Cl
DTH	-I	-H	-Br
DTI	-I	-H	-F
DTJ	-I	-H	$-CH_3$
DTK	-I	-H	$-CF_3$
DTL	-I	-H	$-OCH_3$
DTM	-I	-H	$-OCH_2CH_3$
DTN	-I	-H	$-OCF_3$
DTO	-I	-H	-*tert*-butyl
DTP	-I	-H	-*iso*-propyl

Table 16



(Ig)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
DTQ	-Cl	-Cl	-H
DTR	-Cl	-Br	-H
DTS	-Cl	-F	-H
DTT	-Cl	$-CH_3$	-H
DTU	-Cl	$-CF_3$	-H
DTV	-Cl	$-OCH_3$	-H
DTW	-Cl	$-OCH_2CH_3$	-H
DTX	-Cl	$-OCF_3$	-H
DTY	-Cl	-*tert*-butyl	-H
DTZ	-Cl	-*iso*-propyl	-H
DUA	-Cl	$-CH_3$	$-CH_3$
DUB	-Cl	-H	-H
DUC	-Cl	-H	$-CH_3$
DUD	-Cl	-H	$-CF_3$
DUE	-Cl	-H	$-OCH_3$
DUF	-Cl	-H	$-OCH_2CH_3$
DUG	-Cl	-H	$-OCF_3$
DUH	-Cl	-H	-*tert*-butyl
DUI	-Cl	-H	-*iso*-propyl
DUJ	-Cl	-H	$-OCF_3$
DUK	-Cl	-H	-*tert*-butyl
DUL	-Cl	-H	-*iso*-propyl
DUM	$-CH_3$	-Cl	-H
DUN	$-CH_3$	-Br	-H

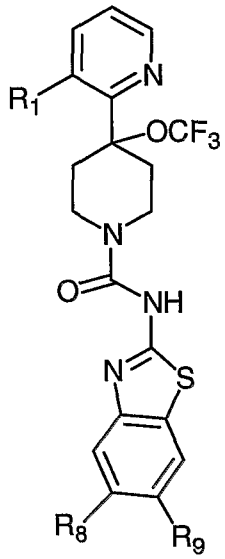
DUO	$-CH_3$	-F	-H
DUP	$-CH_3$	$-CH_3$	-H
DUQ	$-CH_3$	$-CF_3$	-H
DUR	$-CH_3$	$-OCH_3$	-H
DUS	$-CH_3$	$-OCH_2CH_3$	-H
DUT	$-CH_3$	$-OCF_3$	-H
DUU	$-CH_3$	*-tert*-butyl	-H
DUV	$-CH_3$	*-iso*-propyl	-H
DUW	$-CH_3$	$-CH_3$	$-CH_3$
DUX	$-CH_3$	-H	-H
DUY	$-CH_3$	-H	-Cl
DUZ	$-CH_3$	-H	-Br
DVA	$-CH_3$	-H	-F
DVB	$-CH_3$	-H	$-CH_3$
DVC	$-CH_3$	-H	$-CF_3$
DVD	$-CH_3$	-H	$-OCH_3$
DVE	$-CH_3$	-H	$-OCH_2CH_3$
DVF	$-CH_3$	-H	$-OCF_3$
DVG	$-CH_3$	-H	*-tert*-butyl
DVH	$-CH_3$	-H	*-iso*-propyl
DVI	$-CF_3$	-Cl	-H
DVJ	$-CF_3$	-Br	-H
DVK	$-CF_3$	-F	-H
DVL	$-CF_3$	$-CH_3$	-H
DVM	$-CF_3$	$-CF_3$	-H
DVN	$-CF_3$	$-OCH_3$	-H
DVO	$-CF_3$	$-OCH_2CH_3$	-H
DVP	$-CF_3$	$-OCF_3$	-H
DVQ	$-CF_3$	*-tert*-butyl	-H
DVR	$-CF_3$	*-iso*-propyl	-H
DVS	$-CF_3$	$-CH_3$	$-CH_3$
DVT	$-CF_3$	-H	-H
DVU	$-CF_3$	-H	-Cl
DVV	$-CF_3$	-H	-Br
DVW	$-CF_3$	-H	-F
DVX	$-CF_3$	-H	$-CH_3$
DVY	$-CF_3$	-H	$-CF_3$
DVZ	$-CF_3$	-H	$-OCH_3$
DWA	$-CF_3$	-H	$-OCH_2CH_3$
DWB	$-CF_3$	-H	$-OCF_3$
DWC	$-CF_3$	-H	*-tert*-butyl
DWD	$-CF_3$	-H	*-iso*-propyl
DWE	$-CHF_2$	-Cl	-H
DWF	$-CHF_2$	-Br	-H
DWG	$-CHF_2$	-F	-H
DWH	$-CHF_2$	$-CH_3$	-H
DWI	$-CHF_2$	$-CF_3$	-H
DWJ	$-CHF_2$	$-OCH_3$	-H

DWK	$-CHF_2$	$-OCH_2CH_3$	-H
DWL	$-CHF_2$	$-OCF_3$	-H
DWM	$-CHF_2$	*-tert*-butyl	-H
DWN	$-CHF_2$	*-iso*-propyl	-H
DWO	$-CHF_2$	$-CH_3$	$-CH_3$
DWP	$-CHF_2$	-H	-H
DWQ	$-CHF_2$	-H	-Cl
DWR	$-CHF_2$	-H	-Br
DWS	$-CHF_2$	-H	-F
DWT	$-CHF_2$	-H	$-CH_3$
DWU	$-CHF_2$	-H	$-CF_3$
DWV	$-CHF_2$	-H	$-OCH_3$
DWW	$-CHF_2$	-H	$-OCH_2CH_3$
DWX	$-CHF_2$	-H	$-OCF_3$
DWY	$-CHF_2$	-H	*-tert*-butyl
DWZ	$-CHF_2$	-H	*-iso*-propyl
DXA	-OH	-Cl	-H
DXB	-OH	-Br	-H
DXC	-OH	-F	-H
DXD	-OH	$-CH_3$	-H
DXE	-OH	$-CF_3$	-H
DXF	-OH	$-OCH_3$	-H
DXG	-OH	$-OCH_2CH_3$	-H
DXH	-OH	$-OCF_3$	-H
DXI	-OH	*-tert*-butyl	-H
DXJ	-OH	*-iso*-propyl	-H
DXK	-OH	$-CH_3$	$-CH_3$
DXL	-OH	-H	-H
DXM	-OH	-H	-Cl
DXN	-OH	-H	-Br
DXO	-OH	-H	-F
DXP	-OH	-H	$-CH_3$
DXQ	-OH	-H	$-CF_3$
DXR	-OH	-H	$-OCH_3$
DXS	-OH	-H	$-OCH_2CH_3$
DXT	-OH	-H	$-OCF_3$
DXU	-OH	-H	*-tert*-butyl
DXV	-OH	-H	*-iso*-propyl
DXW	$-NO_2$	-Cl	-H
DXX	$-NO_2$	-Br	-H
DXY	$-NO_2$	-F	-H
DXZ	$-NO_2$	$-CH_3$	-H
DYA	$-NO_2$	$-CF_3$	-H
DYB	$-NO_2$	$-OCH_3$	-H
DYC	$-NO_2$	$-OCH_2CH_3$	-H
DYD	$-NO_2$	$-OCF_3$	-H
DYE	$-NO_2$	*-tert*-butyl	-H
DYF	$-NO_2$	*-iso*-propyl	-H

DYG	$-NO_2$	$-CH_3$	$-CH_3$
DYH	$-NO_2$	-H	-H
DYI	$-NO_2$	-H	-Cl
DYJ	$-NO_2$	-H	-Br
DYK	$-NO_2$	-H	-F
DYL	$-NO_2$	-H	$-CH_3$
DYM	$-NO_2$	-H	$-CF_3$
DYN	$-NO_2$	-H	$-OCH_3$
DYO	$-NO_2$	-H	$-OCH_2CH_3$
DYP	$-NO_2$	-H	$-OCF_3$
DYQ	$-NO_2$	-H	*-tert*-butyl
DYR	$-NO_2$	-H	*-iso*-propyl
DYS	-CN	-Br	-H
DYT	-CN	-Cl	-H
DYU	-CN	-F	-H
DYV	-CN	$-CH_3$	-H
DYW	-CN	$-CF_3$	-H
DYX	-CN	$-OCH_3$	-H
DYY	-CN	$-OCH_2CH_3$	-H
DYZ	-CN	$-OCF_3$	-H
DZA	-CN	*-tert*-butyl	-H
DZB	-CN	*-iso*-propyl	-H
DZC	-CN	$-CH_3$	$-CH_3$
DZD	-CN	-H	-H
DZE	-CN	-H	-Cl
DZF	-CN	-H	-Br
DZG	-CN	-H	-F
DZH	-CN	-H	$-CH_3$
DZI	-CN	-H	$-CF_3$
DZJ	-CN	-H	$-OCH_3$
DZK	-CN	-H	$-OCH_2CH_3$
DZL	-CN	-H	$-OCF_3$
DZM	-CN	-H	*-tert*-butyl
DZN	-CN	-H	*-iso*-propyl
DZO	-Br	-Br	-H
DZP	-Br	-Cl	-H
DZQ	-Br	-F	-H
DZR	-Br	$-CH_3$	-H
DZS	-Br	$-CF_3$	-H
DZT	-Br	$-OCH_3$	-H
DZU	-Br	$-OCH_2CH_3$	-H
DZV	-Br	$-OCF_3$	-H
DZW	-Br	*-tert*-butyl	-H
DZX	-Br	*-iso*-propyl	-H
DZY	-Br	$-CH_3$	$-CH_3$
DZZ	-Br	-H	-H
EAA	-Br	-H	-Cl
EAB	-Br	-H	-Br

EAC	-Br	-H	-F
EAD	-Br	-H	$-CH_3$
EAE	-Br	-H	$-CF_3$
EAF	-Br	-H	$-OCH_3$
EAG	-Br	-H	$-OCH_2CH_3$
EAH	-Br	-H	$-OCF_3$
EAI	-Br	-H	-*tert*-butyl
EAJ	-Br	-H	-*iso*-propyl
EAK	-I	-Cl	-H
EAL	-I	-Br	-H
EAM	-I	-F	-H
EAN	-I	$-CH_3$	-H
EAO	-I	$-CF_3$	-H
EAP	-I	$-OCH_3$	-H
EAQ	-I	$-OCH_2CH_3$	-H
EAR	-I	$-OCF_3$	-H
EAS	-I	-*tert*-butyl	-H
EAT	-I	-*iso*-propyl	-H
EAU	-I	$-CH_3$	$-CH_3$
EAV	-I	-H	-H
EAW	-I	-H	-Cl
EAX	-I	-H	-Br
EAY	-I	-H	-F
EAZ	-I	-H	$-CH_3$
EBA	-I	-H	$-CF_3$
EBB	-I	-H	$-OCH_3$
EBC	-I	-H	$-OCH_2CH_3$
EBD	-I	-H	$-OCF_3$
EBE	-I	-H	-*tert*-butyl
EBF	-I	-H	-*iso*-propyl

Table 17



(Ih)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
EBG	-Cl	-Cl	-H
EBH	-Cl	-Br	-H
EBI	-Cl	-F	-H
EBJ	-Cl	$-CH_3$	-H
EBK	-Cl	$-CF_3$	-H
EBL	-Cl	$-OCH_3$	-H
EBM	-Cl	$-OCH_2CH_3$	-H
EBN	-Cl	$-OCF_3$	-H
EBO	-Cl	-*tert*-butyl	-H
EBP	-Cl	-*iso*-propyl	-H
EBQ	-Cl	$-CH_3$	$-CH_3$
EBR	-Cl	-H	-H
EBS	-Cl	-H	$-CH_3$
EBT	-Cl	-H	$-CF_3$
EBU	-Cl	-H	$-OCH_3$
EBV	-Cl	-H	$-OCH_2CH_3$
EBW	-Cl	-H	$-OCF_3$
EBX	-Cl	-H	-*tert*-butyl
EBY	-Cl	-H	-*iso*-propyl
EBZ	-Cl	-H	$-OCF_3$
ECA	-Cl	-H	-*tert*-butyl
ECB	-Cl	-H	-*iso*-propyl
ECC	$-CH_3$	-Cl	-H
ECD	$-CH_3$	-Br	-H

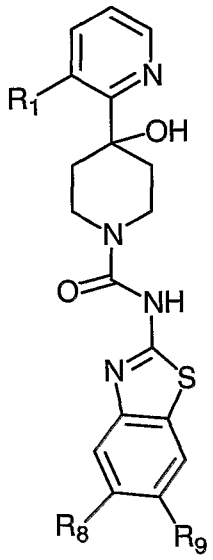
ECE	$-CH_3$	-F	-H
ECF	$-CH_3$	$-CH_3$	-H
ECG	$-CH_3$	$-CF_3$	-H
ECH	$-CH_3$	$-OCH_3$	-H
ECI	$-CH_3$	$-OCH_2CH_3$	-H
ECJ	$-CH_3$	$-OCF_3$	-H
ECK	$-CH_3$	*-tert*-butyl	-H
ECL	$-CH_3$	*-iso*-propyl	-H
ECM	$-CH_3$	$-CH_3$	$-CH_3$
ECN	$-CH_3$	-H	-H
ECO	$-CH_3$	-H	-Cl
ECP	$-CH_3$	-H	-Br
ECQ	$-CH_3$	-H	-F
ECR	$-CH_3$	-H	$-CH_3$
ECS	$-CH_3$	-H	$-CF_3$
ECT	$-CH_3$	-H	$-OCH_3$
ECU	$-CH_3$	-H	$-OCH_2CH_3$
ECV	$-CH_3$	-H	$-OCF_3$
ECW	$-CH_3$	-H	*-tert*-butyl
ECX	$-CH_3$	-H	*-iso*-propyl
ECY	$-CF_3$	-Cl	-H
ECZ	$-CF_3$	-Br	-H
EDA	$-CF_3$	-F	-H
EDB	$-CF_3$	$-CH_3$	-H
EDC	$-CF_3$	$-CF_3$	*-H*
EDD	$-CF_3$	$-OCH_3$	-H
EDE	$-CF_3$	$-OCH_2CH_3$	-H
EDF	$-CF_3$	$-OCF_3$	-H
EDG	$-CF_3$	*-tert*-butyl	-H
EDH	$-CF_3$	*-iso*-propyl	-H
EDI	$-CF_3$	$-CH_3$	$-CH_3$
EDJ	$-CF_3$	-H	-H
EDK	$-CF_3$	-H	-Cl
EDL	$-CF_3$	-H	-Br
EDM	$-CF_3$	-H	-F
EDN	$-CF_3$	-H	$-CH_3$
EDO	$-CF_3$	-H	$-CF_3$
EDP	$-CF_3$	-H	$-OCH_3$
EDQ	$-CF_3$	-H	$-OCH_2CH_3$
EDR	$-CF_3$	-H	$-OCF_3$
EDS	$-CF_3$	-H	*-tert*-butyl
EDT	$-CF_3$	-H	*-iso*-propyl
EDU	$-CHF_2$	-Cl	-H
EDV	$-CHF_2$	-Br	-H
EDW	$-CHF_2$	-F	-H
EDX	$-CHF_2$	$-CH_3$	-H
EDY	$-CHF_2$	$-CF_3$	-H
EDZ	$-CHF_2$	$-OCH_3$	-H

EEA	$-CHF_2$	$-OCH_2CH_3$	-H
EEB	$-CHF_2$	$-OCF_3$	-H
EEC	$-CHF_2$	-*tert*-butyl	-H
EED	$-CHF_2$	-*iso*-propyl	-H
EEE	$-CHF_2$	$-CH_3$	$-CH_3$
EEF	$-CHF_2$	-H	-H
EEG	$-CHF_2$	-H	-Cl
EEH	$-CHF_2$	-H	-Br
EEI	$-CHF_2$	-H	-F
EEJ	$-CHF_2$	-H	$-CH_3$
EEK	$-CHF_2$	-H	$-CF_3$
EEL	$-CHF_2$	-H	$-OCH_3$
EEM	$-CHF_2$	-H	$-OCH_2CH_3$
EEN	$-CHF_2$	-H	$-OCF_3$
EEO	$-CHF_2$	-H	-*tert*-butyl
EEP	$-CHF_2$	-H	-*iso*-propyl
EEQ	-OH	-Cl	-H
EER	-OH	-Br	-H
EES	-OH	-F	-H
EET	-OH	$-CH_3$	-H
EEU	-OH	$-CF_3$	-H
EEV	-OH	$-OCH_3$	-H
EEW	-OH	$-OCH_2CH_3$	-H
EEX	-OH	$-OCF_3$	-H
EEY	-OH	-*tert*-butyl	-*H*
EEZ	-OH	-*iso*-propyl	-H
EFA	-OH	$-CH_3$	$-CH_3$
EFB	-OH	-H	-H
EFC	-OH	-H	-Cl
EFD	-OH	-H	-Br
EFE	-OH	-H	-F
EFF	-OH	-H	$-CH_3$
EFG	-OH	-H	$-CF_3$
EFH	-OH	-H	$-OCH_3$
EFI	-OH	-H	$-OCH_2CH_3$
EFJ	-OH	-H	$-OCF_3$
EFK	-OH	-H	-*tert*-butyl
EFL	-OH	-H	-*iso*-propyl
EFM	$-NO_2$	-Cl	-H
EFN	$-NO_2$	-Br	-H
EFO	$-NO_2$	-F	-H
EFP	$-NO_2$	$-CH_3$	-H
EFQ	$-NO_2$	$-CF_3$	-H
EFR	$-NO_2$	$-OCH_3$	-H
EFS	$-NO_2$	$-OCH_2CH_3$	-H
EFT	$-NO_2$	$-OCF_3$	-H
EFU	$-NO_2$	-*tert*-butyl	-H
EFV	$-NO_2$	-*iso*-propyl	-H

EFW	$-NO_2$	$-CH_3$	$-CH_3$
EFX	$-NO_2$	-H	-H
EFY	$-NO_2$	-H	-Cl
EFZ	$-NO_2$	-H	-Br
EGA	$-NO_2$	-H	-F
EGB	$-NO_2$	-H	$-CH_3$
EGC	$-NO_2$	-H	$-CF_3$
EGD	$-NO_2$	-H	$-OCH_3$
EGE	$-NO_2$	-H	$-OCH_2CH_3$
EGF	$-NO_2$	-H	$-OCF_3$
EGG	$-NO_2$	-H	*-tert*-butyl
EGH	$-NO_2$	-H	*-iso*-propyl
EGI	-CN	-Br	-H
EGJ	-CN	-Cl	-H
EGK	-CN	-F	-H
EGL	-CN	$-CH_3$	-H
EGM	-CN	$-CF_3$	-H
EGN	-CN	$-OCH_3$	-H
EGO	-CN	$-OCH_2CH_3$	-H
EGP	-CN	$-OCF_3$	-H
EGQ	-CN	*-tert*-butyl	-H
EGR	-CN	*-iso*-propyl	-H
EGS	-CN	$-CH_3$	$-CH_3$
EGT	-CN	-H	-H
EGU	-CN	-H	-Cl
EGV	-CN	-H	-Br
EGW	-CN	-H	-F
EGX	-CN	-H	$-CH_3$
EGY	-CN	-H	$-CF_3$
EGZ	-CN	-H	$-OCH_3$
EHA	-CN	-H	$-OCH_2CH_3$
EHB	-CN	-H	$-OCF_3$
EHC	-CN	-H	*-tert*-butyl
EHD	-CN	-H	*-iso*-propyl
EHE	-Br	-Br	-H
EHF	-Br	-Cl	-H
EHG	-Br	-F	-H
EHH	-Br	$-CH_3$	-H
EHI	-Br	$-CF_3$	-H
EHJ	-Br	$-OCH_3$	-H
EHK	-Br	$-OCH_2CH_3$	-H
EHL	-Br	$-OCF_3$	-H
EHM	-Br	*-tert*-butyl	-H
EHN	-Br	*-iso*-propyl	-H
EHO	-Br	$-CH_3$	$-CH_3$
EHP	-Br	-H	-H
EHQ	-Br	-H	-Cl
EHR	-Br	-H	-Br

EHS	-Br	-H	-F
EHT	-Br	-H	$-CH_3$
EHU	-Br	-H	$-CF_3$
EHV	-Br	-H	$-OCH_3$
EHW	-Br	-H	$-OCH_2CH_3$
EHX	-Br	-H	$-OCF_3$
EHY	-Br	-H	*-tert*-butyl
EHZ	-Br	-H	*-iso*-propyl
EIA	-I	-Cl	-H
EIB	-I	-Br	-H
EIC	-I	-F	-H
EID	-I	$-CH_3$	-H
EIE	-I	$-CF_3$	-H
EIF	-I	$-OCH_3$	-H
EIG	-I	$-OCH_2CH_3$	-H
EIH	-I	$-OCF_3$	-H
EII	-I	*-tert*-butyl	-H
EIJ	-I	*-iso*-propyl	-H
EIK	-I	$-CH_3$	$-CH_3$
EIL	-I	-H	-H
EIM	-I	-H	-Cl
EIN	-I	-H	-Br
EIO	-I	-H	-F
EIP	-I	-H	$-CH_3$
EIQ	*-I*	*-H*	*$-CF_3$*
EIR	-I	-H	$-OCH_3$
EIS	-I	-H	$-OCH_2CH_3$
EIT	-I	-H	$-OCF_3$
EIU	-I	-H	*-tert*-butyl
EIV	-I	-H	*-iso*-propyl

Table 18



(Ii)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8	R_9
EIW	-Cl	-Cl	-H
EIX	-Cl	-Br	-H
EIY	-Cl	-F	-H
EIZ	-Cl	$-CH_3$	-H
EJA	-Cl	$-CF_3$	-H
EJB	-Cl	$-OCH_3$	-H
EJC	-Cl	$-OCH_2CH_3$	-H
EJD	-Cl	$-OCF_3$	-H
EJE	-Cl	-*tert*-butyl	-H
EJF	-Cl	-*iso*-propyl	-H
EJG	-Cl	$-CH_3$	$-CH_3$
EJH	-Cl	-H	-H
EJI	-Cl	-H	$-CH_3$
EJJ	-Cl	-H	$-CF_3$
EJK	-Cl	-H	$-OCH_3$
EJL	-Cl	-H	$-OCH_2CH_3$
EJM	-Cl	-H	$-OCF_3$
EJN	-Cl	-H	-*tert*-butyl
EJO	-Cl	-H	-*iso*-propyl
EJP	-Cl	-H	$-OCF_3$
EJQ	-Cl	-H	-*tert*-butyl
EJR	-Cl	-H	-*iso*-propyl
EJS	$-CH_3$	-Cl	-H
EJT	$-CH_3$	-Br	-H

EJU	$-CH_3$	-F	-H
EJV	$-CH_3$	$-CH_3$	-H
EJW	$-CH_3$	$-CF_3$	-H
EJX	$-CH_3$	$-OCH_3$	-H
EJY	$-CH_3$	$-OCH_2CH_3$	-H
EJZ	$-CH_3$	$-OCF_3$	-H
EKA	$-CH_3$	*-tert*-butyl	-H
EKB	$-CH_3$	*-iso*-propyl	-H
EKC	$-CH_3$	$-CH_3$	$-CH_3$
EKD	$-CH_3$	-H	-H
EKE	$-CH_3$	-H	-Cl
EKF	$-CH_3$	-H	-Br
EKG	$-CH_3$	-H	-F
EKH	$-CH_3$	-H	$-CH_3$
EKI	$-CH_3$	-H	$-CF_3$
EKJ	$-CH_3$	-H	$-OCH_3$
EKK	$-CH_3$	-H	$-OCH_2CH_3$
EKL	$-CH_3$	-H	$-OCF_3$
EKM	$-CH_3$	-H	*-tert*-butyl
EKN	$-CH_3$	-H	*-iso*-propyl
EKO	$-CF_3$	-Cl	-H
EKP	$-CF_3$	-Br	-H
EKQ	$-CF_3$	-F	-H
EKR	$-CF_3$	$-CH_3$	-H
EKS	$-CF_3$	$-CF_3$	-H
EKT	$-CF_3$	$-OCH_3$	-H
EKU	$-CF_3$	$-OCH_2CH_3$	-H
EKV	$-CF_3$	$-OCF_3$	-H
EKW	$-CF_3$	*-tert*-butyl	-H
EKX	$-CF_3$	*-iso*-propyl	-H
EKY	$-CF_3$	$-CH_3$	$-CH_3$
EKZ	$-CF_3$	-H	-H
ELA	$-CF_3$	-H	-Cl
ELB	$-CF_3$	-H	-Br
ELC	$-CF_3$	-H	-F
ELD	$-CF_3$	-H	$-CH_3$
ELE	$-CF_3$	-H	$-CF_3$
ELF	$-CF_3$	-H	$-OCH_3$
ELG	$-CF_3$	-H	$-OCH_2CH_3$
ELH	$-CF_3$	-H	$-OCF_3$
ELI	$-CF_3$	-H	*-tert*-butyl
ELJ	$-CF_3$	-H	*-iso*-propyl
ELK	$-CHF_2$	-Cl	-H
ELL	$-CHF_2$	-Br	-H
ELM	$-CHF_2$	-F	-H
ELN	$-CHF_2$	$-CH_3$	-H
ELO	$-CHF_2$	$-CF_3$	-H
ELP	$-CHF_2$	$-OCH_3$	-H

ELQ	$-CHF_2$	$-OCH_2CH_3$	-H
ELR	$-CHF_2$	$-OCF_3$	-H
ELS	$-CHF_2$	-*tert*-butyl	-H
ELT	$-CHF_2$	-*iso*-propyl	-H
ELU	$-CHF_2$	$-CH_3$	$-CH_3$
ELV	$-CHF_2$	-H	-H
ELW	$-CHF_2$	-H	-Cl
ELX	$-CHF_2$	-H	-Br
ELY	$-CHF_2$	-H	-F
ELZ	$-CHF_2$	-H	$-CH_3$
EMA	$-CHF_2$	-H	$-CF_3$
EMB	$-CHF_2$	-H	$-OCH_3$
EMC	$-CHF_2$	-H	$-OCH_2CH_3$
EMD	$-CHF_2$	-H	$-OCF_3$
EME	$-CHF_2$	-H	-*tert*-butyl
EMF	$-CHF_2$	-H	-*iso*-propyl
EMG	-OH	-Cl	-H
EMH	-OH	-Br	-H
EMI	-OH	-F	-H
EMJ	-OH	$-CH_3$	-H
EMK	-OH	$-CF_3$	-H
EML	-OH	$-OCH_3$	-H
EMM	-OH	$-OCH_2CH_3$	-H
EMN	-OH	$-OCF_3$	-H
EMO	*-OH*	*-tert-butyl*	*-H*
EMP	-OH	-*iso*-propyl	-H
EMQ	-OH	$-CH_3$	$-CH_3$
EMR	-OH	-H	-H
EMS	-OH	-H	-Cl
EMT	-OH	-H	-Br
EMU	-OH	-H	-F
EMV	-OH	-H	$-CH_3$
EMW	-OH	-H	$-CF_3$
EMX	-OH	-H	$-OCH_3$
EMY	-OH	-H	$-OCH_2CH_3$
EMZ	-OH	-H	$-OCF_3$
ENA	-OH	-H	-*tert*-butyl
ENB	-OH	-H	-*iso*-propyl
ENC	$-NO_2$	-Cl	-H
END	$-NO_2$	-Br	-H
ENE	$-NO_2$	-F	-H
ENF	$-NO_2$	$-CH_3$	-H
ENG	$-NO_2$	$-CF_3$	-H
ENH	$-NO_2$	$-OCH_3$	-H
ENI	$-NO_2$	$-OCH_2CH_3$	-H
ENJ	$-NO_2$	$-OCF_3$	-H
ENK	$-NO_2$	-*tert*-butyl	-H
ENL	$-NO_2$	-*iso*-propyl	-H

ENM	$-NO_2$	$-CH_3$	$-CH_3$
ENN	$-NO_2$	-H	-H
ENO	$-NO_2$	-H	-Cl
ENP	$-NO_2$	-H	-Br
ENQ	$-NO_2$	-H	-F
ENR	$-NO_2$	-H	$-CH_3$
ENS	$-NO_2$	-H	$-CF_3$
ENT	$-NO_2$	-H	$-OCH_3$
ENU	$-NO_2$	-H	$-OCH_2CH_3$
ENV	$-NO_2$	-H	$-OCF_3$
ENW	$-NO_2$	-H	*-tert*-butyl
ENX	$-NO_2$	-H	*-iso*-propyl
ENY	-CN	-Br	-H
ENZ	-CN	-Cl	-H
EOA	-CN	-F	-H
EOB	-CN	$-CH_3$	-H
EOC	-CN	$-CF_3$	-H
EOD	-CN	$-OCH_3$	-H
EOE	-CN	$-OCH_2CH_3$	-H
EOF	-CN	$-OCF_3$	-H
EOG	-CN	*-tert*-butyl	-H
EOH	-CN	*-iso*-propyl	-H
EOI	-CN	$-CH_3$	$-CH_3$
EOJ	-CN	-H	-H
EOK	-CN	-H	-Cl
EOL	-CN	-H	-Br
EOM	-CN	-H	-F
EON	-CN	-H	$-CH_3$
EOO	-CN	-H	$-CF_3$
EOP	-CN	-H	$-OCH_3$
EOQ	-CN	-H	$-OCH_2CH_3$
EOR	-CN	-H	$-OCF_3$
EOS	-CN	-H	*-tert*-butyl
EOT	-CN	-H	*-iso*-propyl
EOU	-Br	-Br	-H
EOV	-Br	-Cl	-H
EOW	-Br	-F	-H
EOX	-Br	$-CH_3$	-H
EOY	-Br	$-CF_3$	-H
EOZ	-Br	$-OCH_3$	-H
EPA	-Br	$-OCH_2CH_3$	-H
EPB	-Br	$-OCF_3$	-H
EPC	-Br	*-tert*-butyl	-H
EPD	-Br	*-iso*-propyl	-H
EPE	-Br	$-CH_3$	$-CH_3$
EPF	-Br	-H	-H
EPG	-Br	-H	-Cl
EPH	-Br	-H	-Br

EPI	-Br	-H	-F
EPJ	-Br	-H	$-CH_3$
EPK	-Br	-H	$-CF_3$
EPL	-Br	-H	$-OCH_3$
EPM	-Br	-H	$-OCH_2CH_3$
EPN	-Br	-H	$-OCF_3$
EPO	-Br	-H	-*tert*-butyl
EPP	-Br	-H	-*iso*-propyl
EPQ	-I	-Cl	-H
EPR	-I	-Br	-H
EPS	-I	-F	-H
EPT	-I	$-CH_3$	-H
EPU	-I	$-CF_3$	-H
EPV	-I	$-OCH_3$	-H
EPW	-I	$-OCH_2CH_3$	-H
EPX	-I	$-OCF_3$	-H
EPY	-I	-*tert*-butyl	-H
EPZ	-I	-*iso*-propyl	-H
EQA	-I	$-CH_3$	$-CH_3$
EQB	-I	-H	-H
EQC	-I	-H	-Cl
EQD	-I	-H	-Br
EQE	-I	-H	-F
EQF	-I	-H	$-CH_3$
EQG	-I	-H	$-CF_3$
EQH	-I	-H	$-OCH_3$
EQI	-I	-H	$-OCH_2CH_3$
EQJ	-I	-H	$-OCF_3$
EQK	-I	-H	-*tert*-butyl
EQL	-I	-H	-*iso*-propyl

4.5 DEFINITIONS

As used herein, the terms used above having following meaning:

"-(C_1-C_{10})alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain -(C_1-C_{10})alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl, and -n-decyl. Representative branched -(C_1-C_{10})alkyls include -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -*iso*-pentyl, -*neo*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

"-(C_1-C_6)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative straight chain -(C_1-C_6)alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl. Representative branched -(C_1-C_6)alkyls include -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -*iso*-pentyl, -*neo*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethtylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, and 3,3-dimethylbutyl.

"-(C_1-C_4)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 4 carbon atoms. Representative straight chain -(C_1-C_4)alkyls include -methyl, -ethyl, -n-propyl, and -n-butyl. Representative branched -(C_1-C_4)alkyls include -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, and -*tert*-butyl.

"-(C_2-C_{10})alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_{10})alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -*iso*-butylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl,

-3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like.

"-(C_2-C_6)alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_6)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -*iso*-butylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, 3-hexenyl and the like.

"-(C_2-C_{10})alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched -(C_2-C_{10})alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonynyl, -2-nonynyl, -8-nonynyl, -1-decynyl, -2-decynyl, -9-decynyl and the like.

"-(C_2-C_6)alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched (C_2-C_6)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl and the like.

"-(C_3-C_{10})cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 10 carbon atoms. Representative (C_3-C_{10})cycloalkyls are -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl, and -cyclodecyl.

"-(C_3-C_8)cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C_3-C_8)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, and -cyclooctyl.

"-(C_8-C_{14})bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_8-C_{14})bicycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

"-(C_8-C_{14})tricycloalkyl" means a tri-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated ring. Representative -(C_8-C_{14})tricycloalkyls include -pyrenyl, -1,2,3,4-tetrahydroanthracenyl,

-perhydroanthracenyl, -aceanthreneyl, -1,2,3,4-tetrahydropenanthrenyl, -5,6,7,8-tetrahydrophenanthrenyl, perhydrophenanthrenyl and the like.

"-(C_5-C_{10})cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms. Representative (C_5-C_{10})cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl and the like.

"-(C_5-C_8)cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 8 carbon atoms. Representative -(C_5-C_8)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl and the like.

"-(C_8-C_{14})bicycloalkenyl" means a bi-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms. Representative -(C_8-C_{14})bicycloalkenyls include -indenyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl, -1,2,7,8-tetrahydronaphthalenyl and the like.

"-(C_8-C_{14})tricycloalkenyl" means a tri-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms. Representative -(C_8-C_{14})tricycloalkenyls include -anthracenyl, -phenanthrenyl, -phenalenyl, -acenaphthalenyl, *as*-indacenyl, *s*-indacenyl and the like.

"-(3- to 7-membered)heterocycle" or "-(3- to 7-membered)heterocyclo" means a 3- to 7-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3- or a 4-membered heterocycle can contain up to 3 heteroatoms, a 5-membered heterocycle can contain up to 4 heteroatoms, a 6-membered heterocycle can contain up to 6 heteroatoms, and a 7-membered heterocycle can contain up to 7 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 7-membered)heteroaryl can be attached via a nitrogen or carbon atom. Representative -(3- to 7-membered)heteroaryls include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl,

tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and the like.

"-(3- to 5-membered)heterocycle" or "-(3- to 5-membered)heterocyclo" means a 3- to 5-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3- or a 4-membered heterocycle can contain up to 3 heteroatoms, and a 5-membered heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 5-membered)heteroaryl can be attached via a nitrogen or carbon atom. Representative -(3- to 5-membered)heteroaryls include furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, triazinyl, pyrrolidinonyl, pyrrolidinyl, hydantoinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl and the like.

"-(7- to 10-membered)bicycloheterocycle" or "-(7- to 10-membered)bicycloheterocyclo" means a 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A -(7- to 10-membered)bicycloheterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(7- to 10-membered)bicycloheterocycle can be attached via a nitrogen or carbon atom. Representative -(7- to 10-membered)bicycloheterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, -benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, -β-carbolinyl and the like.

"-(C_{14})aryl" means a 14-membered aromatic carbocyclic moiety such as -anthryl or -phenanthryl.

"-(5- to 10-membered)heteroaryl" means an aromatic heterocycle ring of 5 to 10 members, including both mono- and bicyclic ring systems, where at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. In one embodiment, one of the -(5- to 10-membered)heteroaryl's rings contain at least one carbon atom. In another embodiment, both of the -(5- to 10-membered)heteroaryl's rings contain at least one carbon atom. Representative -(5- to 10-membered)heteroaryls include pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl,

pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

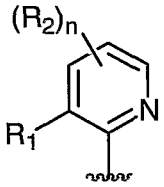
"-CH_2(halo)" means a methyl group where one of the hydrogens of the methyl group has been replaced with a halogen. Representative -CH_2(halo) groups include -CH_2F, -CH_2Cl, -CH_2Br, and -CH_2I.

"-$CH(halo)_2$" means a methyl group where two of the hydrogens of the methyl group have been replaced with a halogen. Representative -$CH(halo)_2$ groups include -CHF_2, -$CHCl_2$, -$CHBr_2$, CHBrCl, CHClI, and -CHI_2.

"-$C(halo)_3$" means a methyl group where each of the hydrogens of the methyl group has been replaced with a halogen. Representative -$C(halo)_3$ groups include -CF_3, -CCl_3, -CBr_3, and -CI_3.

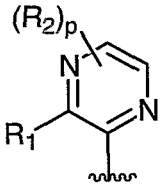
"-Halogen" or "-Halo" means -F, -Cl, -Br, or -I.

The phrase "pyridyl group" means



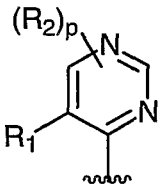
where R_1, R_2, and n are defined above for the Piperidine Compounds.

The phrase "pyrazinyl group" means,



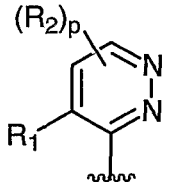
where R_1, R_2, and p are defined above for the Piperidine Compounds.

The phrase "pyrimidinyl group" means



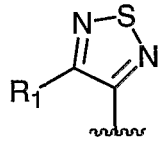
where R_1, R_2, and p are defined above for the Piperidine Compounds.

The phrase "pyridazinyl group" means



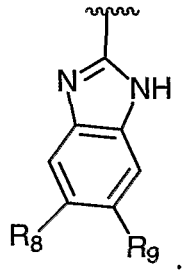
where R_1, R_2, and p are defined above for the Piperidine Compounds.

The phrase "thiazanyl group" means



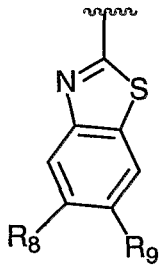
where R_1 is defined above for the Piperidine Compounds.

The phrase "benzoimidiazolyl group " means



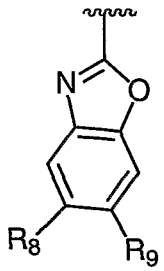
where R_8 and R_9 are defined above for the Piperidine Compounds.

The phrase "benzothiazolyl group" means



where R_8 and R_9 are defined above for the Piperidine Compounds.

The phrase "benzooxazolyl group" means



where R_8 and R_9 are defined above for the Piperidine Compounds.

The term "animal," includes, but is not limited to, a cow, monkey, baboon, chimpanzee, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig, and human.

The phrase "pharmaceutically acceptable salt," as used herein, is any pharmaceutically acceptable salt that can be prepared from a Piperidine Compound, including a salt formed from an acid and a basic functional group, such as a nitrogen group, of one of the Piperidine Compounds. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also includes a salt prepared from a Piperidine Compound having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-*tert*-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine and the like.

The phrase "effective amount," when used in connection with a Piperidine Compound means an amount effective for: (a) treating or preventing a Condition; or (b) inhibiting VR1, mGluR1, or mGluR5 function in a cell.

The phrase "effective amount," when used in connection with the another therapeutic agent means an amount for providing the therapeutic effect of the therapeutic agent.

When a first group is "substituted with one or more" second groups, one or more hydrogen atoms of the first group is replaced with a corresponding number of second groups. When the number of second groups is two or greater, each second group can be the same or different. In one embodiment, the number of second groups is one or two. In another embodiment, the number of second groups is one.

The term "THF" means tetrahydrofuran.

The term "DCM" means dichloromethane.

The term "DMF" means dimethylformamide.

The term "DAST" means "(diethylamino) sulfur trifluoride.

The term "DMSO" means dimethyl sulfoxide.

The term "IBD" means inflammatory-bowel disease.

The term "IBS" means irritable-bowel syndrome.

The term "ALS" means amyotrophic lateral sclerosis.

The phrases "treatment of," "treating" and the like include the amelioration or cessation of a Condition or a symptom thereof.

In one embodiment, treating includes inhibiting, for example, decreasing the overall frequency of episodes of a Condition or a symptom thereof.

The phrases "prevention of," "preventing" and the like include the avoidance of the onset of a Condition or a symptom thereof.

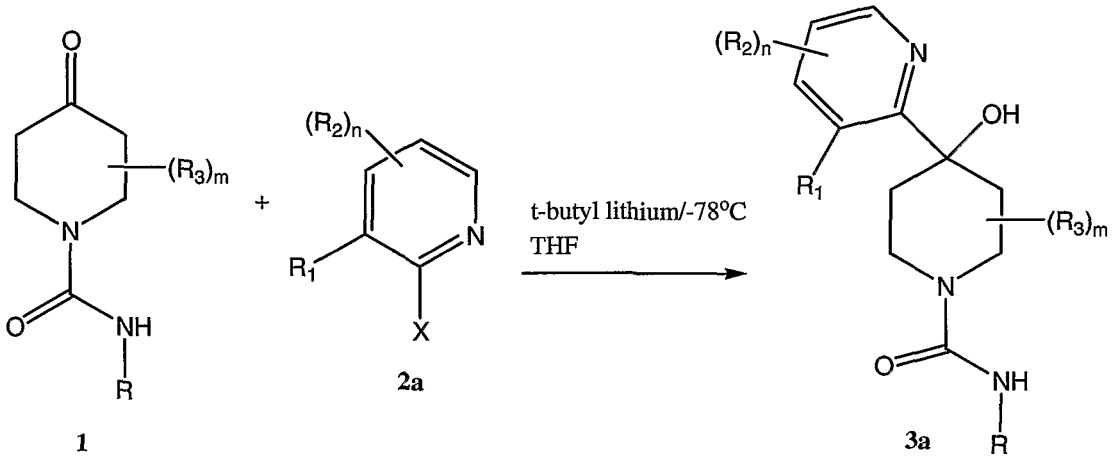
4.6 METHODS FOR MAKING THE PIPERIDINE COMPOUNDS

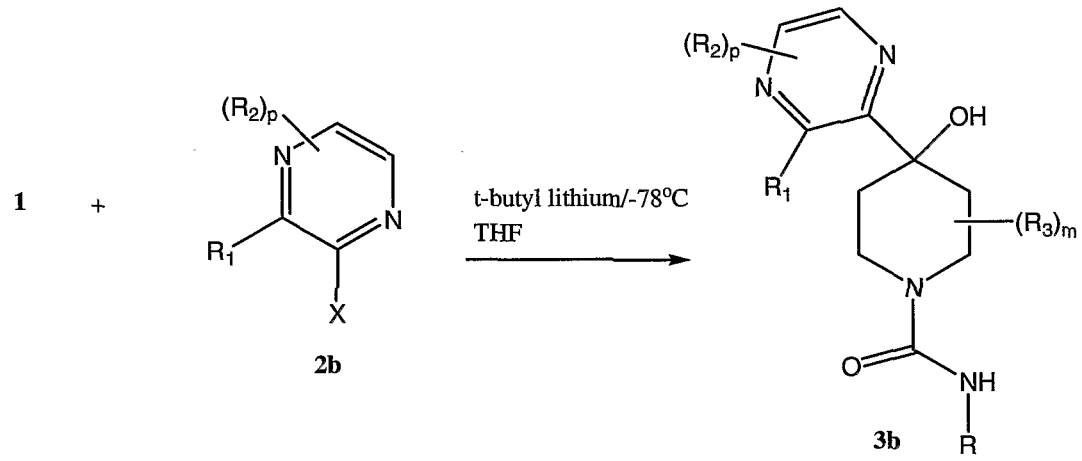
The Piperidine Compounds can be made using conventional organic synthesis or by the following illustrative methods shown in the schemes below.

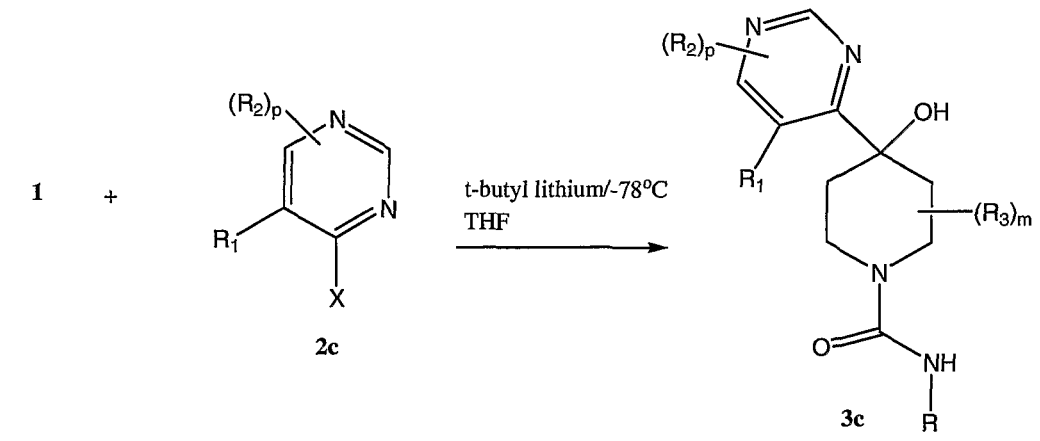
4.6.1 Methods for Making the Piperidine Compounds Where X is O and R_4 is -OH

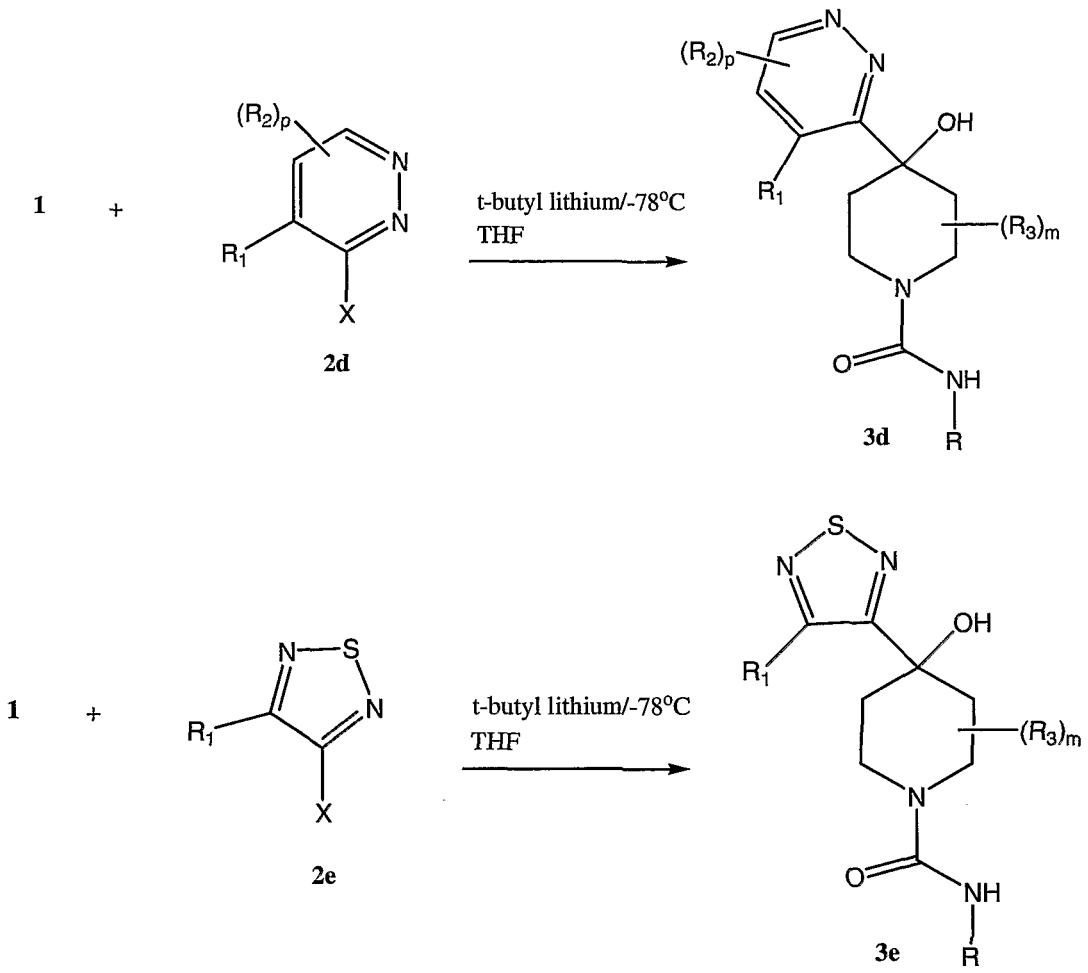
The Piperidine Compounds where X is O and R_4 is -OH can be obtained by the illustrative method shown below in Scheme **1:**

Scheme 1


O
(R3)m
N
O
NH
R
1
+
(R2)n
N
R1
X
2a
t-butyl lithium/-78°C
THF
(R2)n
N
OH
R1
(R3)m
N
O
NH
R
3a


1
+
(R2)p
N
N
R1
X
2b
t-butyl lithium/-78°C
THF
(R2)p
N
N
OH
R1
(R3)m
N
O
NH
R
3b


1
+
(R2)p
N
N
R1
X
2c
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THF
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N
N
OH
R1
(R3)m
N
O
NH
R
3c



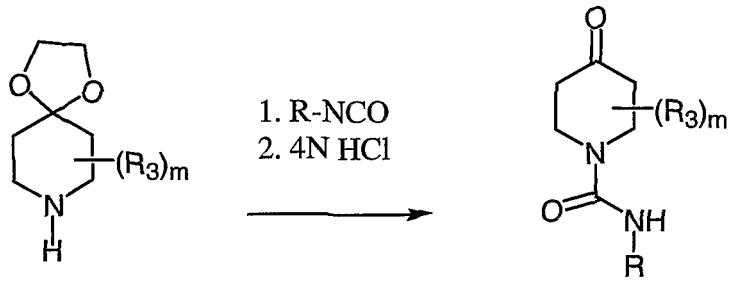
where R_1, R_2, R_3, n, m, and p are defined above for the Piperidine Compounds; R is Ar_2 or Ar_3; and X is a halogen.

To a solution of a compound of formula **2a-e** in the presence of *tert*-butyl lithium (1.7 M in heptane, 6.45 mL, 11.12 mmol) in THF (20 mL) at -78°C is added dropwise a compound of formula **1** in anhydrous THF (10 mL). The resulting reaction mixture is stirred at -78°C for about 3 h and is quenched with aqueous NH_4Cl at about 0°C and the organic and aqueous layers separated. The aqueous layer is extracted with THF, the organic layers combined, and the combined organic layers dried (Na_2SO_4). The resulting solution is concentrated under reduced pressure to provide a residue. The residue is purified using flash chromatography on a silica gel column eluted with ethyl acetate/hexane (gradient elution from 30:70 to 70:30) to provide a Piperidine Compound where X is O and R_4 is -OH (**3a-e**).

The compounds of formula **2a-e** are commercially available or can be prepared by methods known to those skilled in the art.

The compound of formula **1** can be obtained by reacting a compound of formula **4** with an isocyanate as shown below in Scheme **2**.

Scheme 2

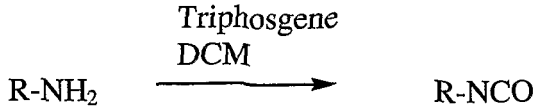


4 **1**

where R_3, and m are defined above for the Piperidine Compounds; and R is Ar_2 or Ar_3.

A compound of formula **4** (20 mmol) in chloroform is added to a solution of an isocyanate of formula R-NCO in chloroform (30 mL) at about 25°C. The resultant reaction mixture is stirred for about 3 h at about 25°C. The solvent is then removed under reduced pressure to provide a residue. The residue is suspended in THF (50 mL) and 4N HCl (50 mL) is added to the resulting solution and the reaction mixture allowed to stir for about 12 h. The reaction mixture is then poured into water (200 mL) and the pH adjusted to a value greater than 10 with aqueous potassium carbonate. The resulting solution is extracted with ethyl acetate and the ethyl acetate layers are combined and dried ($MgSO_4$). The solvent is then removed under reduced pressure to provide a residue that can be purified using flash chromatography on a silica gel column eluted with ethyl acetate/hexane (gradient elution from 30:70 to 70:30) to provide the compound of formula **1**.

Isocyanates of formula R-NCO are commercially available or are can be prepared by reacting an amine RNH_2 with phosgene according to known methods (*See, e.g.*, H. Eckert and B. Foster, *Angew. Chem. Int. Ed. Engl.*, 26, 894 (1987); H. Eckert, Ger. Offen. DE 3 440 141; *Chem. Abstr.* 106, 4294d (1987); and L. Contarca et al., *Synthesis*, 553-576 (1996). For example, an amine Ar_2NH_2 can be reacted with triphosgene according to the scheme shown below.



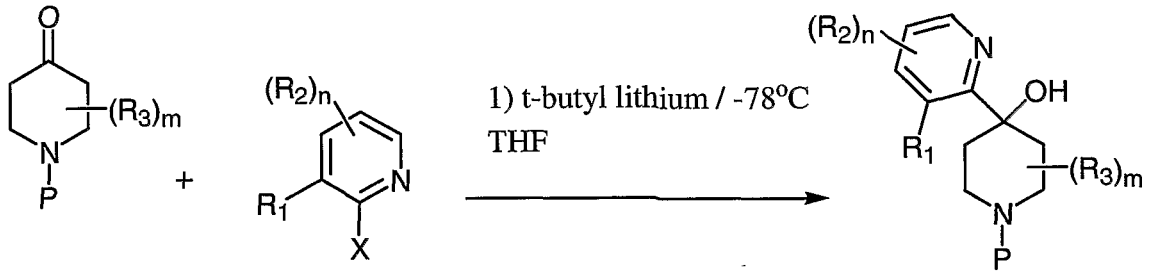
Typically a solution of triphosgene (about 0.3 eq.) in DCM (about 0.3M) is slowly added to a stirred solution of the amine (about 1.0 eq.) in DCM (about 0.3M) at

about about 25°C. The reaction mixture is then stirred at about about 25°C for about 10 min. and the temperature then raised to about 70°C. After stirring at about 70°C for about 3 h., the reaction mixture is cooled to about about 25°C, filtered, and the filtrate concentrated to give the desired isocyanate.

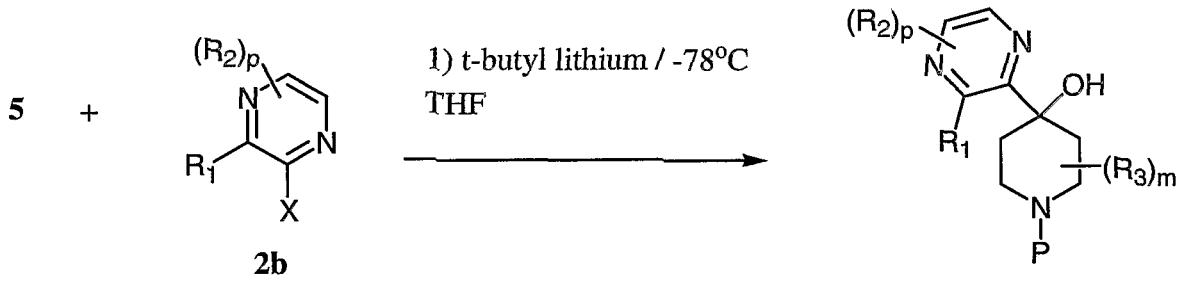
Compounds of formula **4** are commercially avaialable or can be prepared by methods known to those skilled in the art.

The Piperidine Compounds where X is O and R_4 is -OH can also be obtained by the illustrative method shown below in Schemes **3** and **4.**

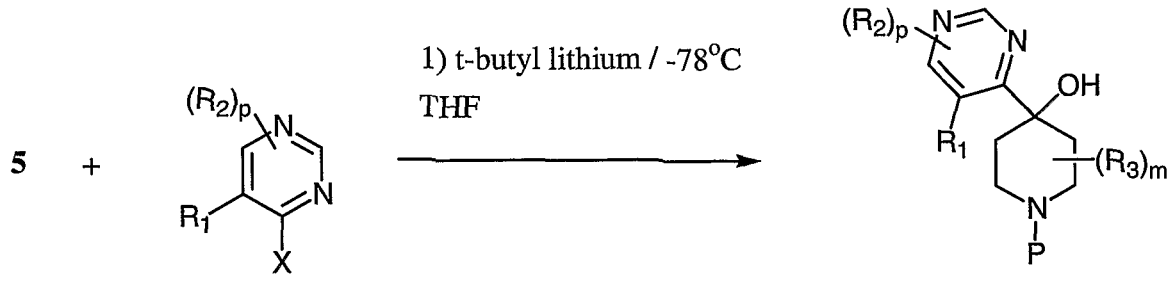
Scheme 3



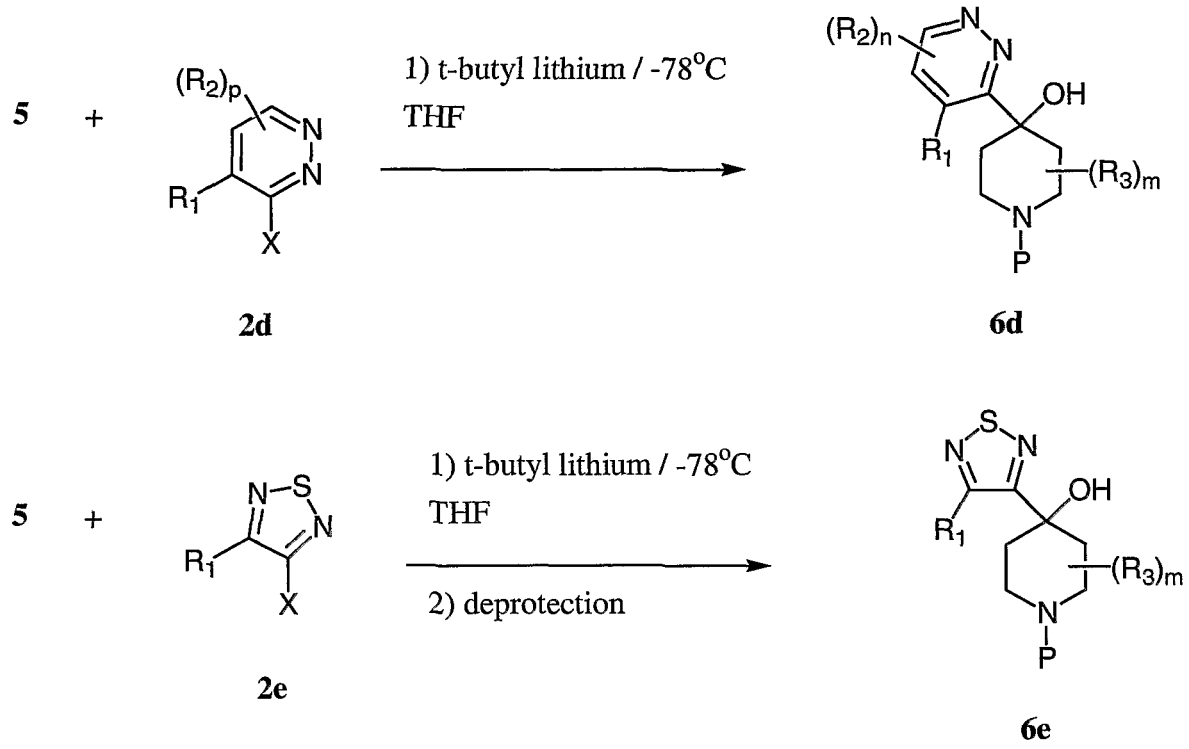
5 **2a** **6a**



2b **6b**



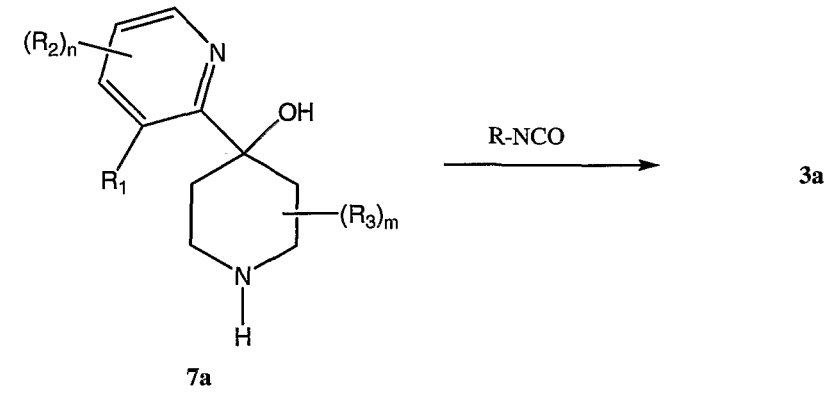
2c **6c**



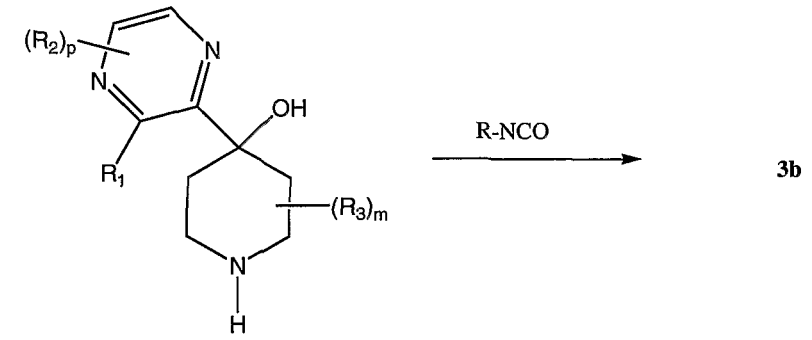
where R_1, R_2, R_3, n, m, and p are defined above for the Piperidine Compounds; X is a halogen; and P is a nitrogen protecting group (see, for example, T.W. Greene et al., *Protective Groups in Organic Synthesis* 494-653 (3d ed. 1999).

To a solution of t-BuLi (1.7 M in heptane, 18.4 mL, 31.3 mmol) or n-BuLi (1.6 M in heptane, 19.5 mL, 31.3 mmol) in ether (30 mL) is added dropwise a solution of a compound of formula **2a-e** (31.3 mmol) in ether (20 mL) at -78°C under a nitrogen atmosphere. The resulting solution is stirred at -78°C for about 1 hour. To the resulting solution is added dropwise a compound of formula **5** (25.0 mmol) dissolved in ether (20 mL) at -78°C and the resulting mixture is allowed to stir at about -50°C for 3 h. The reaction mixture is then quenched with aqueous NH_4Cl at 0°C and the resulting reaction mixture is extracted with ether. The organic layers are combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a residue that can be purified using flash chromatography on a silica gel column eluted with ethyl acetate/ hexane (gradient elution 30/70 to 70/30) to provide a compound of formula **6a-e**. The nitrogen protecting group is then removed to provide a compound of formula **7a-e**, respectively. The compound of formula **7a-e** is then reacted with an isocyanate of formula R-NCO to provide the compound of formula **3a-e**, as shown below in Scheme 4.

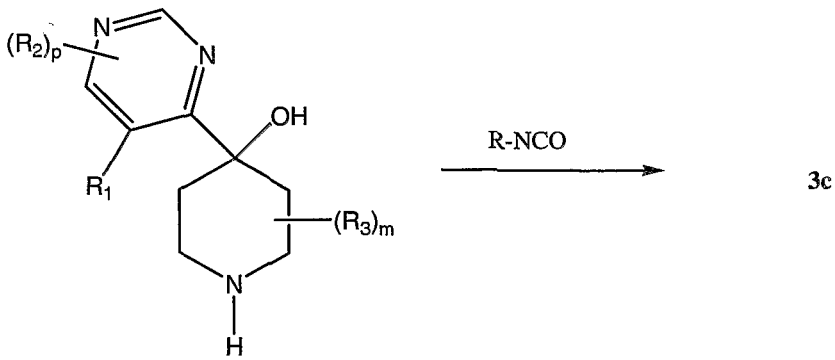
Scheme 4



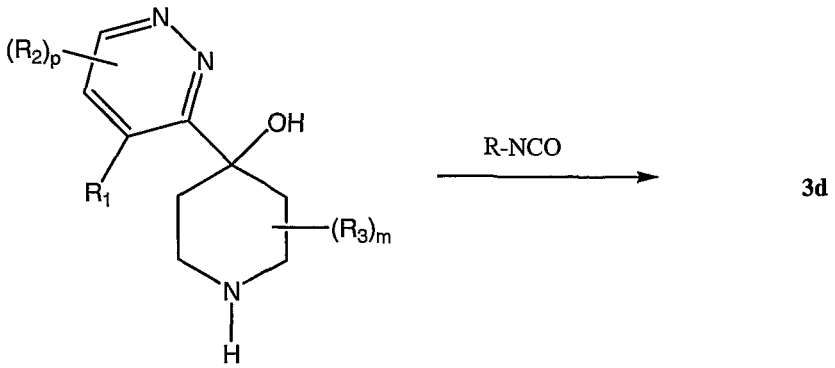
7a



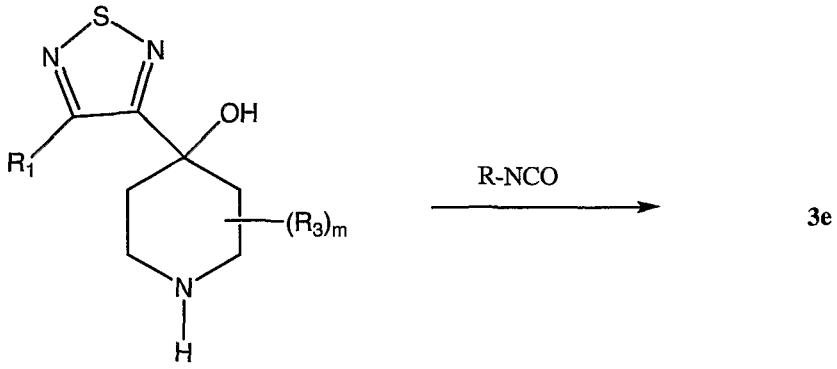
7b



7c



7d

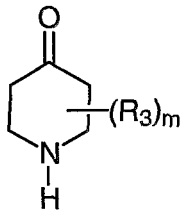


7e

where R_1, R_2, R_3, n, m, and p are defined above for the Piperidine Compounds; R is Ar_2 or Ar_3; and X is a halogen.

To a solution of a compound of formula **7a-e** (1 mmol) in DCM (1 mL) is added dropwise a solution of isocyanate R-NCO (1 mmol) in DCM (1 mL) at the about 25°C. The resultant mixture is allowed to stir at about 25°C for about 3 h. The solvent is then removed under reduced pressure to provide a residue that can be purified using a silica gel column eluted with ethyl acetate/ hexane (gradient elution 10/90 to 70/30) to provide a compound of formula **3a-e.**

A compound of formula **5** is commercially available or can be prepared by protecting the nitrogen atom of a compound of formula **8**, shown below:



8

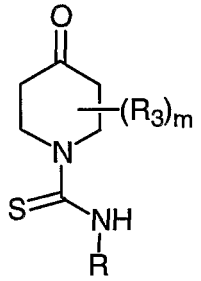
Compounds of formula **8** is commercially available or can be prepared by methods known to those skilled in the art.

Any nitrogen protecting group known to those skilled in the art can be used to protect the nitrogen atom in the compound of formula **8**. Suitable protecting groups are described in T.W. Greene et al., *Protective Groups in Organic Synthesis*, 494-653 (3d ed. 1999).

Isocyanates of formula R-NCO are commercially available or are can be prepared as described above.

4.6.2 Methods for Making Piperidine Compounds Where X is S and R_4 is -OH

The Piperidine Compound where X is S and R_4 is -OH can be obtained by a method analogous to that described in Scheme **1** to provide the Piperidine Compounds where X is O and R_4 is -OH (**3a-e**) except that a compound of formula **9**, shown below,



9

where R_3 and m are defined above for the Piperidine Compounds and R is Ar_2 or Ar_3 is used in place of the compound of formula **1**.

The compound of formula **9** can be obtained by a method analogous to that described in Scheme **2** to provide the compound of formula **1** except that an isothiocyanate of formula R-NCS is used in place of the isocyanate R-NCO.

Isothiocyanates are commercially available or can be prepared by reacting an amine of formula Ar_2NH_2 with thiophosgene as shown in the scheme below (*See, e.g.*, *Tett. Lett.*, 41(37), 7207-7209 (2000); *Org. Prep. Proced., Int.*, 23(6), 729-734 (1991); *J. Heterocycle Chem.*, 28(4), 1091-1097 (1991); *J. Fluorine Chem.*, 41(3), 303-310 (1988); and *Tett. Lett.*, 42(32), 5414-5416 (2001).

$$R\text{-}NH_2 \xrightarrow{C(S)Cl_2} R\text{-}NCS$$

Alternatively, isothiocyanates of formula R-NCS can be prepared by reacting an amine of formula RNH_2 with carbon disulfide in the presence of triethylamine in THF, followed by reaction with hydrogen peroxide and hydrochloric acid in water as shown in the scheme below (*See, e.g., J. Org. Chem.*, 62(13), 4539-4540 (1997)).

1. Et_3N, THF, CS_2
2. H_2O_2
3. HCl, water

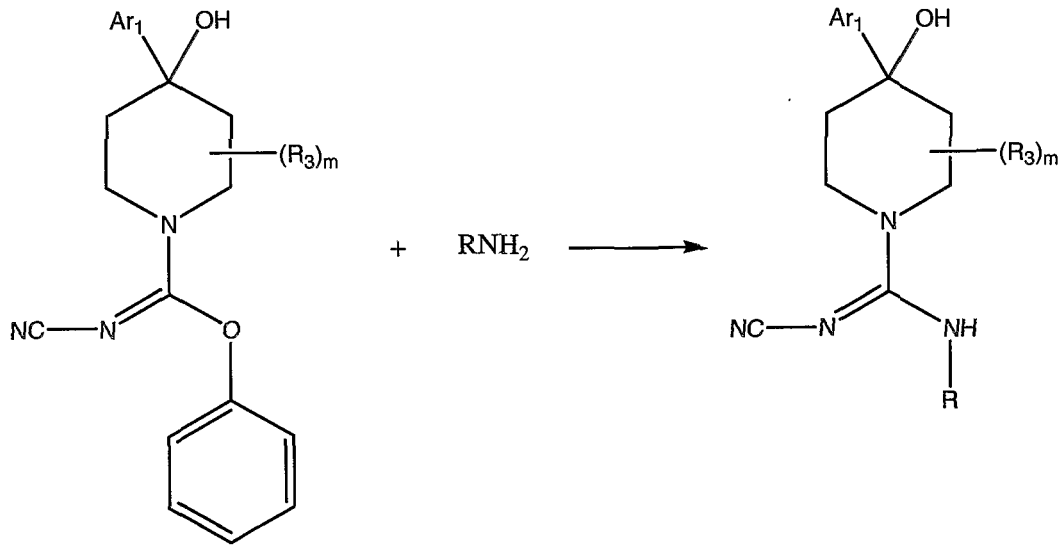
$$R\text{-}NH_2 \longrightarrow R\text{-}NCS$$

The Piperidine Compound where X is S and R_4 is -OH can be obtained by a method analogous to that described in Schemes **3** and **4** to provide the Piperidine Compounds where X is O and R_4 is -OH (**3a-e**) except that an isothiocyanates of formula R-NCS is used in place of the isocyanate of formula R-NCO.

4.6.3 Methods for Making Piperidine Compounds Where X is N-CN and R_4 is -OH

The Piperidine Compound where X is N-CN and R_4 is -OH can be obtained as shown below in Scheme **5**

Scheme 5



10

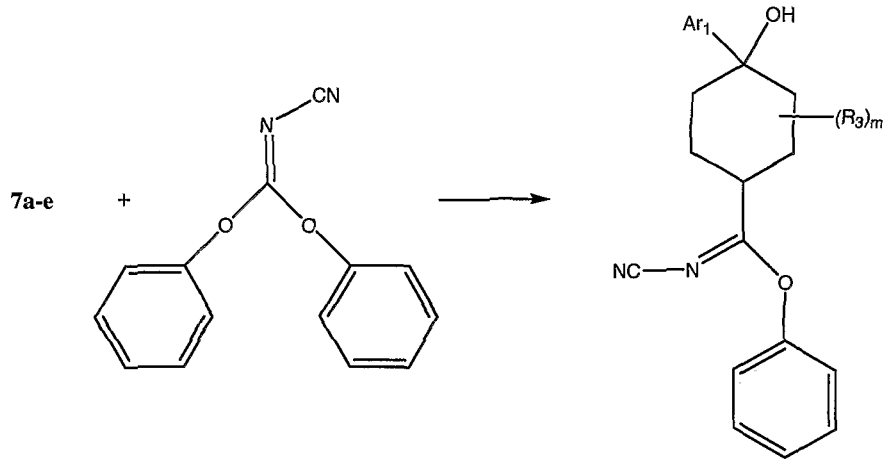
where Ar_1, R_3 and m are defined above for the Piperidine Compounds; and R is Ar_2 or Ar_3.

A compound of formula **10** is reacted with an amine of formula $R\text{-}NH_2$ in an aprotic organic solvent such as diethyl ether, di-n-propyl ether, THF, DCM, or toluene at a temperature ranging from about 25°C to about the reflux temperature of the solvent for a period of about 0.5 h to about 24 h to provide the Piperidine Compound where X is N-CN and R_4 is -OH. In one embodiment, the aprotic organic solvent is di-n-propyl ether. In another embodiment, a reaction mixture of di-n-propyl ether, a compound of

formula **10** and the amine of formula R-NH_2 is heated at a temperature of about 70° to about 80° C. In another embodiment, the reaction mixture of di-n-propyl ether, a compound of formula **10** and the amine of formula R-NH_2 is heated at a temperature of about 75°C for about 12 h.

The compound of formula **10** can be obtained as shown below in Scheme **6**

Scheme 6



10

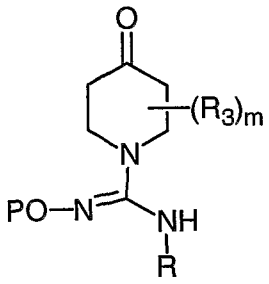
where Ar_1 is defined above for the Piperidine Compounds.

A compound of formula **7a-e** is reacted with diphenylcyanocarbodimidate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in an aprotic solvent such as diethyl ether, di-n-propyl ether, THF, DCM, or toluene to provide the compound of formula **10**. In one embodiment, the aprotic solvent is DCM and the reaction mixture of the compound of formula **7a-e** and diphenylcyanocabonimidate is allowed to react at about 25°C. In another embodiment, the aprotic solvent is toluene and the reaction mixture of the compound of formula **7a-e** and diphenylcyanocarbodimidate is allowed to react at about 110°C. The compound of formula **7a-e** and diphenylcyanocabodimidate is typically allowed to react for a period of about 0.5 h to about 24 h. Typically the compound of formula **10** is used without further purification.

The compounds of formula **7a-e** can be obtained as described above in Section 4.6.1.

4.6.4 Methods for Making Piperidine Compounds Where X is N-OH and R_4 is -OH

The Piperidine Compound where X is N-OH and R_4 is -OH can be prepared by a method analogous to that described in Scheme **1** to provide the Piperidine Compounds where X is O and R_4 is -OH (**3a-e**) except that a compound of formula **11**, shown below,

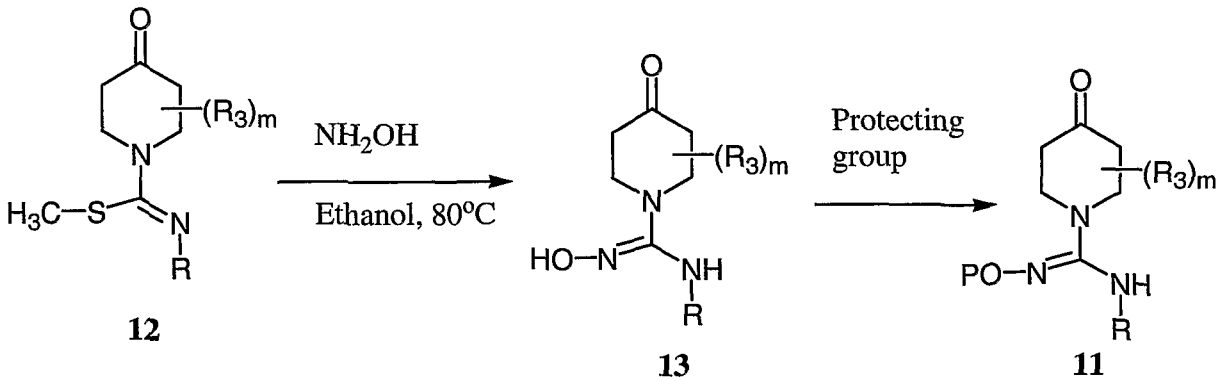


11

where R_3 and m are defined above for the Piperidine Compounds, R is Ar_2 or Ar_3, and P is an oxygen protecting group, is used in place of the compound of formula **1** followed by removal of the oxygen protecting group.

The compound of formula **11** can be obtained as shown below in Scheme **7**

Scheme 7



12 **13** **11**

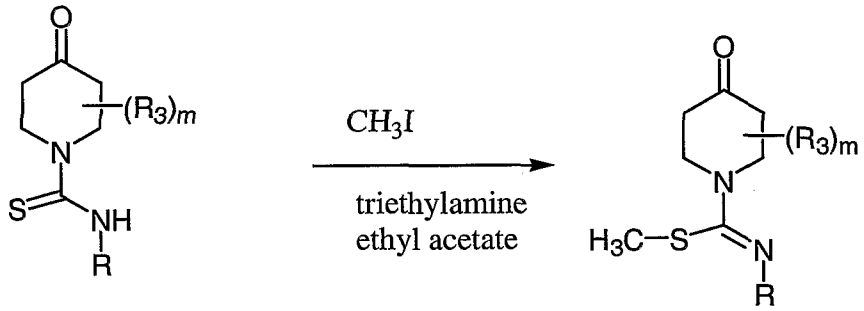
where R_3 and m are defined above for the Piperidine Compounds, R is Ar_2 or Ar_3, and P is a nitrogen protecting group.

A compound of formula **12** (about 0.3 mmol) is reacted with hydroxylamine (50 weight percent in water, about 5.8 mmol) in about 1.5 mL of ethanol with stirring at a temperature of about 80°C for about 2 h. The mixture is then

concentrated under reduced pressure to provide a compound of formula **13**. The hydroxyl group of the compound of formula **13** is then protected using an oxygen protecting group to provide the compound of formula **11**. Any oxygen protecting group known to those skilled in the art can be used to protect the oxygen atom in the compound of formula **13**. Suitable oxygen protecting groups are disclosed in T.W. Greene et al., *Protective Groups in Organic Synthesis* 17-200 (3d ed. 1999). In one embodiment, the compound of formula **11** is purified using column chromatography or recrystallization.

The compound of formula **12** can be obtained as shown below in Scheme **8**

Scheme 8



9 **12**

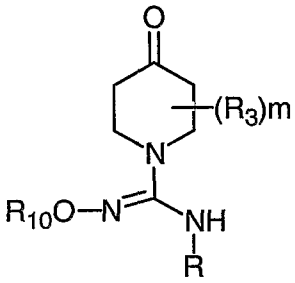
where R_3 and m are defined above for the Piperidine Compounds, and R is Ar_2 or Ar_3.

A solution of a compound of formula **9** (about 0.6 mmol), obtained as described above, in DCM is reacted with iodomethane (about 0.9 mmol) in about 3 mL of tetrahydrofuran with stirring at about 25°C for about 12 h. Excess iodomethane is removed from the mixture using reduced pressure. A solution of triethylamine (about 1.74 mmol) in about 2.5 mL of ethyl acetate is then added to the mixture and the mixture is allowed to stir for about 2 h. The mixture is then concentrated under reduced pressure to provide the compound of formula **12** that can then be purified. In one embodiment, the compound of formula **12** is purified using column chromatography or recrystallization.

4.6.5 Methods for Making Piperidine Compounds Where X is N-OR_{10} and R_4 is -OH

The Piperidine Compound where X is N-OR_{10} and R_4 is -OH can be obtained by a method analogous to that described in Scheme **1** to provide the Piperidine

Compounds where X is O and R_4 is -OH (**3a-e**) except that a compound of formula **14**, shown below,



14

where R_3, R_{10} and m are defined above for the Piperidine Compounds, and R is Ar_2 or Ar_3 is used in place of the compound of formula **1**.

The compound of formula **14** can be prepared by reacting the compound of formula **13**, obtained as described above in Scheme **7**, with X-(C_1-C_4)alkyl, where X is -I, -Br, -Cl, or -F in the presence of sodium hydride in DMF at about 25°C. In one embodiment, X is -I or -Br.

4.6.6 Methods for Making Piperidine Compounds Where R_4 is a Group Other Than -OH

The Piperidine Compounds where R_4 is -halo, -OCF_3, -(C_1C_6)alkyl, -CH_2OH, -CH_2Cl, -CH_2Br, -CH_2I, -CH_2F, -CH(halo)$_2$, -CF_3, -OR_{10}, -SR_{13}, -COOH, -$COOR_{10}$, -$C(O)R_{10}$, -C(O)H, -$OC(O)R_{10}$, -$OC(O)NHR_{10}$, -$NHC(O)R_{13}$, -SO_2R_{10}, -$CON(R_{13})_2$ or -NO_2 can be obtained from the Piperidine Compounds where R_4 is -OH.

The Piperidine Compounds where R_4 is -F can be obtained by reacting a Piperidine Compound where R_4 is -OH with DAST according to the procedure described in M. Schlosser *et al.*, *Tetrahedron* 52(24):8257-62 (1996).

The Piperidine Compounds where R_4 is -Cl can be obtained by reacting a Piperidine Compound where R_4 is -OH with $SOCl_2$ or PCl_5 according to the procedure described in *J. Amer. Chem. Soc.* 120 (4):673-79 (1998) or with CH_3COCl according to the procedure described in *Tett. Lett.* 41(47):9037-42 (2000).

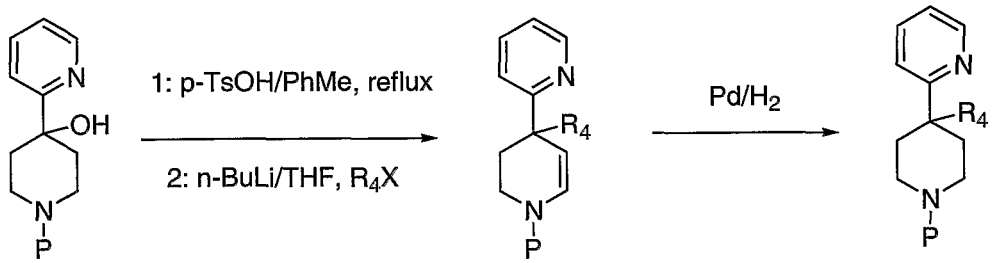
The Piperidine Compounds where R_4 is -Br can be obtained by reacting a Piperidine Compound where R_4 is -OH with pyridine and $SOBr_2$ according to the procedure described in *J. Organometallic Chemistry* 627(2):179-88 (2001) or by reacting

a Piperidine Compound where R_4 is -OH with pyridine and PPh_3/Br_2 according to the procedure described in *J. Amer. Chem. Soc.* 112 (9):3607-14 (1990).

The Piperidine Compounds where R_4 is -I can be obtained by reacting a Piperidine Compound where R_4 is -OH with HI in acetic anhydride according to the procedure described in *J. Amer. Chem. Soc.* 87(3):539-542 (1965).

The Piperidine Compounds where R_4 is $-CH_3$ can be obtained by reacting a Piperidine Compound where R_4 is -OH with PCl_5 and CH_3TiCl_3 according to the procedure described in *Angewandte Chemie*, 92(11), 933-4 (1980).

The Piperidine Compounds where R_4 is $-(C_1\text{-}C_6)$alkyl can be obtained by reacting a Piperidine Compound where R_4 is -OH with p-toluenesulfonic acid in toluene followed by n-butyl lithium and $X\text{-}(C_1\text{-}C_6)$alkyl, where X is a halogen, according to the procedure described in Charles J. Barnett, *et al, J. Org. Chem.*, 54(20) 4795-4800 (1989) followed by hydrogenating the product according to the procedure described in Thomas E. D'Ambra *et al, J. Org. Chem.*, 54(23) 5632-5 (1989) as described in the Scheme below.



The Piperidine Compounds where R_4 is $-CH_2OH$ can be obtained by reacting a Piperidine Compound where R_4 is -COOH with $LiAlH_4$ according to procedures known to those skilled in the art. The Piperidine Compounds where R_4 is $-CH_2OH$ can be obtained by reacting a Piperidine Compound where R_4 is -C(O)H with $NaBH_4$ according to procedures known to those skilled in the art.

The Piperidine Compounds where R_4 is -COOH can be obtained by reacting a Piperidine Compound where R_4 is -CN with KOH according to procedures known to those skilled in the art.

The Piperidine Compounds where R_4 is -CN can be obtained by reacting a Piperidine Compound where R_4 is -OH with KCN and $SOCl_2$ according to the procedure described in *Armyanskii Khimicheskii Zhurnal.* 30(9) 723-7 (1977).

The Piperidine Compounds where R_4 is -C(O)H can be obtained by reacting a Piperidine Compound where R_4 is -CN with di-*iso*-butylaluminum hydride (DIBAL-H) according to procedures known to those skilled in the art.

The Piperidine Compounds where R_4 is $-OCF_3$ can be obtained by reacting a Piperidine Compound where R_4 is -OH with with CS_2; methyl idodide; and bromosuccinimide and pyridine/HF in DCM according to the procedure described in *Chemical Communications (Cambridge)* 3 309-10 (1997) or *Bulletin of the Chemical Society of Japan*, 73(2) 471-484 (2000).

The Piperidine Compounds where R_4 is $-CH_2Cl$ can be obtained by reacting a Piperidine Compound where R_4 is $-CH_2OH$, obtained as described above, with PCl_5 according to the procedure described in *J. Amer. Chem. Soc.*, 120 (4) 673-9 (1998).

The Piperidine Compounds where R_4 is $-CH_2Br$ can be obtained by reacting a Piperidine Compound where R_4 is $-CH_2OH$, obtained as described above, with $SOBr_2$ according to the procedure described in *J. Organomet. Chem.*, 627 (2) 179-88 (2001) or with PPh_3/Br_2 according to the procedure described in *J. Amer. Chem. Soc.*, 112 (9) 3607-14 (1990).

The Piperidine Compounds where R_4 is $-CH_2F$ can be obtained by reacting a Piperidine Compound where R_4 is $-CH_2OH$, obtained as described above, with 1 eq. of DAST according to the procedure described in M. Schlosser *et al.*, *Tetrahedron* 52(24):8257-62 (1996) and *Organic Letters*. 3(17) 2713-15 (2001).

The Piperidine Compounds where R_4 is $-CH_2I$ can be obtained by reacting a Piperidine Compound where R_4 is $-CH_2OH$, obtained as described above, with PPh_3/I_2 according to the procedure described in *Organic Process Research and Development* 6(2) 190-1 (2002).

The Piperidine Compounds where R_4 is $-CH(halo)_2$ can be obtained by reacting a Piperidine Compound where R_4 is -C(O)H, obtained as described above, with $(F_3CSO_2)_2O$ followed by $Mg(halo)_2$ in CS_2 according to the procedure described in *Synthesis* 12 1076-8 (1986).

The Piperidine Compounds where R_4 is $-CHF_2$ can also be obtained by reacting a Piperidine Compound where R_4 is -C(O)H, obtained as described above, with 2 eq. of DAST according to the procedure described in M. Schlosser *et al.*, *Tetrahedron* 52(24):8257-62 (1996) and *Organic Letters*. 3(17) 2713-15 (2001).

The Piperidine Compounds where R_4 is $-CF_3$ can be obtained by reacting a Piperidine Compound where R_4 is -C(O)H, obtained as described above, with copper

(I) iodide and sodium trifluoroacetate according to the procedure described in U.S. Patent No. 4,866,197 to Bauman.

The Piperidine Compounds where R_4 is $-OR_{10}$ can be obtained by reacting a Piperidine Compound where R_4 is -OH, obtained as described above, with R_{10}-X where X is a halogen in the presence of NaOH according to the procedure described in *European Journal of Medicinal Chemistry* 24(4) 391-6 (1989).

The Piperidine Compounds where R_4 is $-SR_{13}$ can be obtained by reacting a Piperidine Compound where R_4 is -OH, obtained as described above, with R_{13}-SH according to the procedure described in U.S. Patent No. 4,409,229 to Ong et al. or *Journal of Medicinal Chemistry* 24(1) 74-9 (1981).

The Piperidine Compounds where R_4 is $-COOR_{10}$ can be obtained by esterifying a Piperidine Compound where R_4 is -COOH, obtained as described above, with R_{10}-OH. Methods to esterify carboxylic acids are known to those skilled in the art.

The Piperidine Compounds where R_4 is $-OC(O)R_{10}$ can be obtained by reacting a Piperidine Compound where R_4 is -OH, obtained as described above, with $R_{10}C(O)Cl$ according to the procedure described in *European Journal of Medicinal Chemistry* 24(4) 391-6 (1989). The acid chlorides, $R_{10}C(O)Cl$, can be prepared from the corresponding carboxylic acid, $R_{10}COOH$, using procedures known to those skilled in the art.

The Piperidine Compounds where R_4 is $-NHC(O)R_{13}$ can be obtained by reacting a Piperidine Compound where R_4 is -OH with $R_{10}CN$ in the presence of H_2SO_4 followed by K_2CO_3 in DCM as described in *Bioorganic and Medicinal Chemistry Letters* 10(17):2001-2014 (2000).

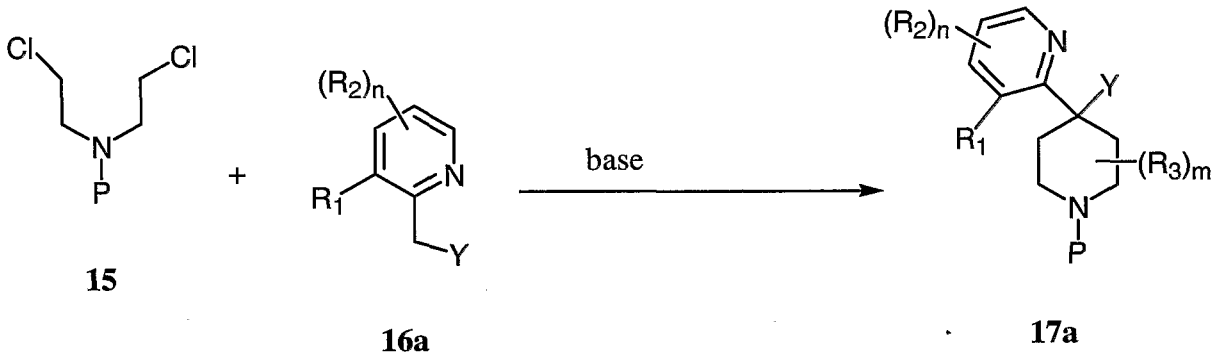
The Piperidine Compounds where R_4 is $-OC(O)NH_2$ can be obtained by reacting a Piperidine Compound where R_4 is -OH with $Cl_3CCONCO$ in DCM at 0°C with stirring for about 2 h and then adding to the resulting mixture K_2CO_3 in methanol-water and allowing the resulting misture to stir for about 4 h at 0°C and about 2 h at about 25°C according to the procedure described in Christopher P. Holmes *et al, J. Org. Chem.*, 54(1) 98-108 (1989).

The Piperidine Compounds where R_4 is $-OC(O)NHR_{10}$ can be obtained by reacting a Piperidine Compound where R_4 is -OH with an isocyanate of formula $R_{10}NCO$ in refluxing THF for about 24 h at about 25°C according to the procedure described in Andre Hallot et al, *J. Med. Chem.*, 29(3) 369-75 (1986).

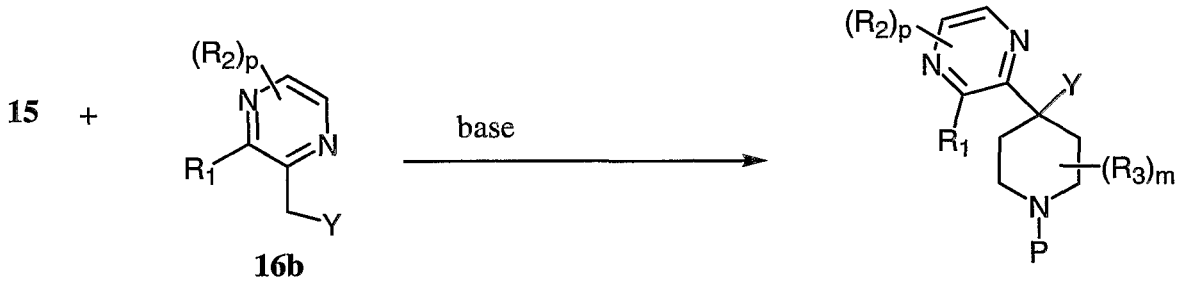
The Piperidine Compounds where R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, and $CON(R_{13})_2$ can be prepared by the illustrative methods described below.

A compound of formula **15** is reacting with a compound of formula **16a-e** in the presence of a base according to the procedure described in *Journal of Heterocycle Chemistry*, 23(1):73-75 (1986) or *Organic Chemistry and Procedures International* 28(4): 478-80 (1996) to provide a compound of formula **17a-e**, as described below in Scheme **9**.

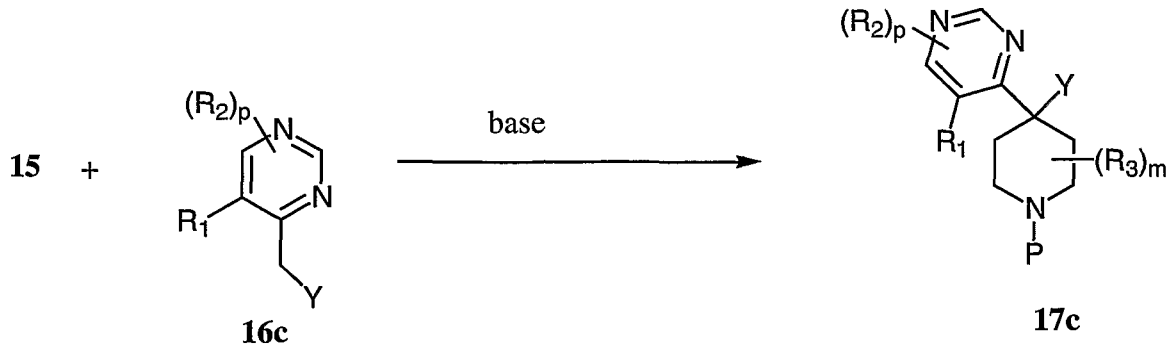
Scheme 9



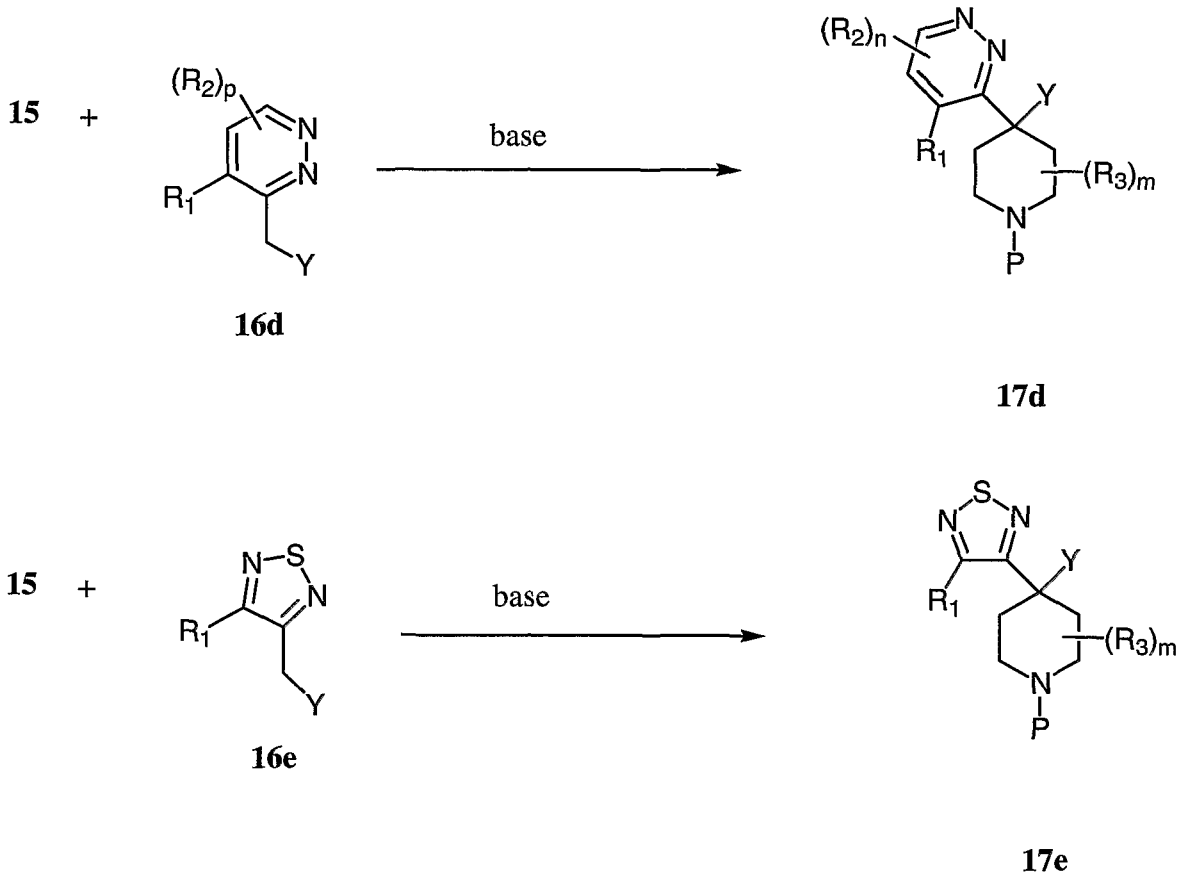
15 **16a** **17a**



16b **17b**



16c **17c**

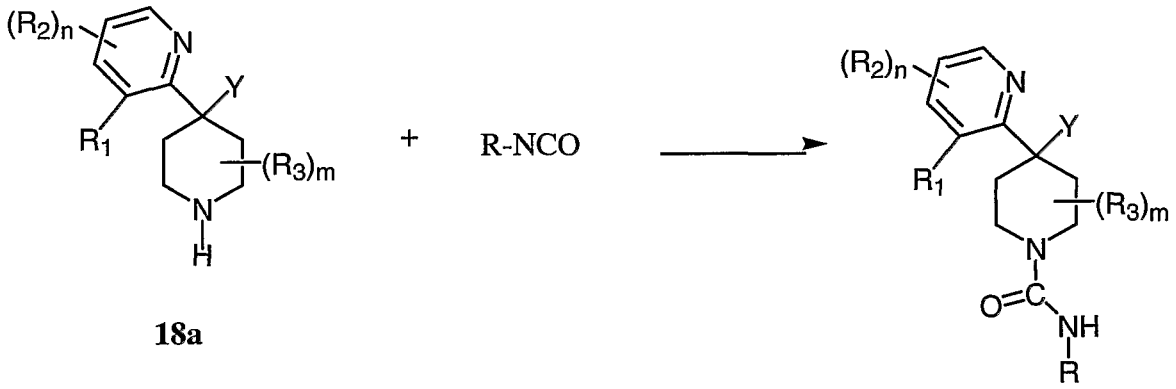


where R_1, R_2, R_3, n, m, and p are defined above for the Piperidine Compounds; Y is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, or $CON(R_{13})_2$; and P is a nitrogen protecting group.

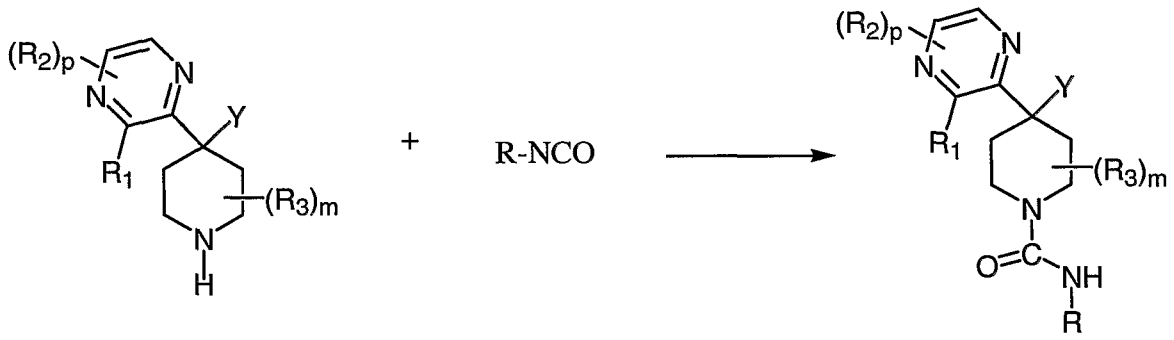
The nitrogen protecting group is then removed from the compound of formula **17a-e** to provide a compound of formula **18a-e**. Any nitrogen protecting group known to those skilled in the art can be used to protect the nitrogen in the compound of formula **15**.

To provide the Piperidine Compounds of formula (I) where X is O and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, or $CON(R_{13})_2$, the compound of formula **18a-e** is then reacted with an isocyanate of formula R-NCO according to a procedure analogous to that described above in Scheme **4** and described below in Scheme **10**.

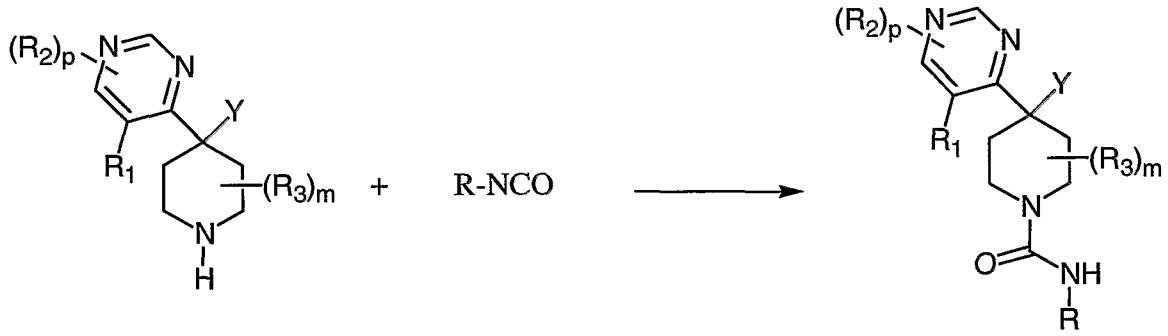
Scheme 10



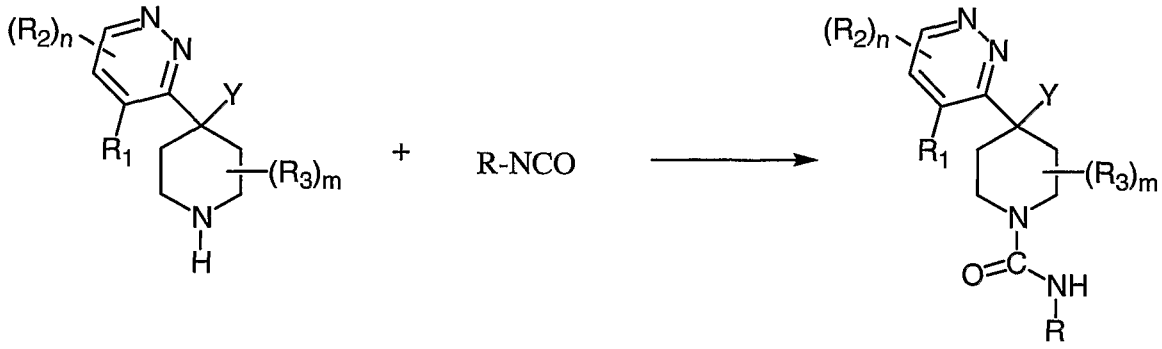
18a



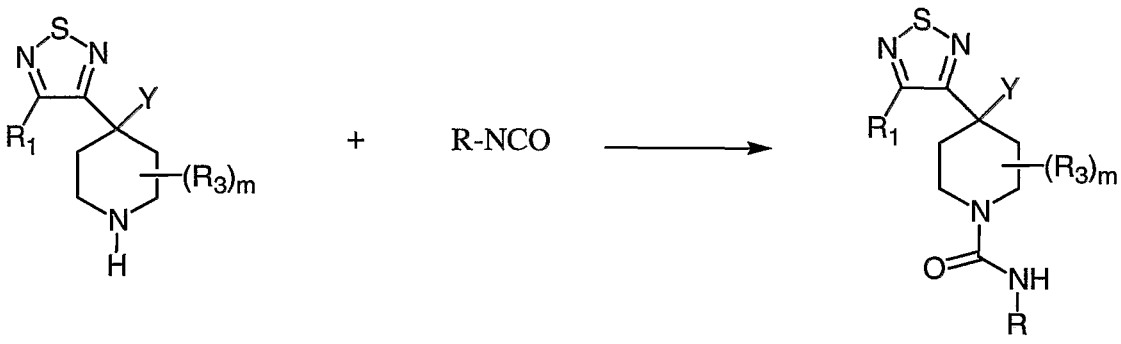
18b



18c



18d



18e

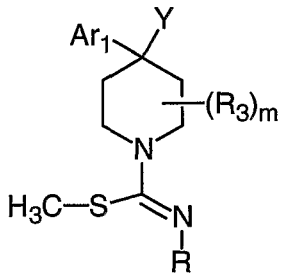
where R_1, R_2, R_3, n, m, and p are defined above for the Piperidine Compounds; Y is $-SO_2R_{10}$, $-NO_2$, $-COR_{10}$, or $-CON(R_{13})_2$; and R is Ar_2 or Ar_3.

A compound of formula **18a-e** is reacted with a compound of formula R-NCO according to a procedure analogous to that described in Scheme **4**.

To provide the Piperidine Compounds where X is S and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, or $CON(R_{13})_2$, the compound of formula **18a-e** is reacted with an isothiocyanate of formula R-NCS according to a procedure analogous to that described above in Section 4.6.2.

To provide the Piperidine Compounds where X is N-CN and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, or $CON(R_{13})_2$, the compound of formula **18a-e** is reacted with diphenylcyanocarbodimidate and then an amine of formula $R-NH_2$ according to a procedure analogous to that described above in Section 4.6.3.

To provide the Piperidine Compounds where X is N-OH and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, or $CON(R_{13})_2$, the Piperidine Compound where X is S and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, and $CON(R_{13})_2$ is reacted with methyl iodide according to a procedure analogous to that described above in Scheme **8** to provide a compound of formula **19**



19

where Ar_1, R_3, m, and Y are defined above for the Piperidine Compounds, and R is Ar_2 or Ar_3.

The compound of formula **19** is then reacted with hydroxylamine in ethanol according to a procedure analogous to that described above in Scheme **8** to provide the Piperidine Compounds where X is N-OH and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, or $CON(R_{13})_2$.

To provide the Piperidine Compounds where X is $N-OR_{10}$ and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, or $CON(R_{13})_2$, the Piperidine Compound where X is NOH and R_4 is $-SO_2R_{10}$, $-NO_2$, -CN, $-COR_{10}$, $-COOR_{10}$, and $CON(R_{13})_2$ is reacted with $X-(C_1-C_4)$alkyl, where X is -I, -Br, -Cl, or -F in the presence of triethylamine according to a procedure analogous to that described above in Section 4.6.6.

The compound of formula **15** is commercially available or can be prepared by methods known to those skilled in the art.

The compounds of formula **16a-e** where Y is $-SO_2R_{10}$ can be obtained by reacting a compound of formula **16a-e**, where Y is a halogen, with $R_{10}SO_2H$ according to the procedure described in *J. Org. Chem.* 67(13): 4387-91 (2002) or international publication no. WO 02/48098.

The compounds of formula **16a-e** where Y is -CN can be obtained by reacting a compound of formula **16a-e**, where Y is a halogen, with potassium cyanide according to the procedure described in *Farmaco* 45(9): 945-53 (1990).

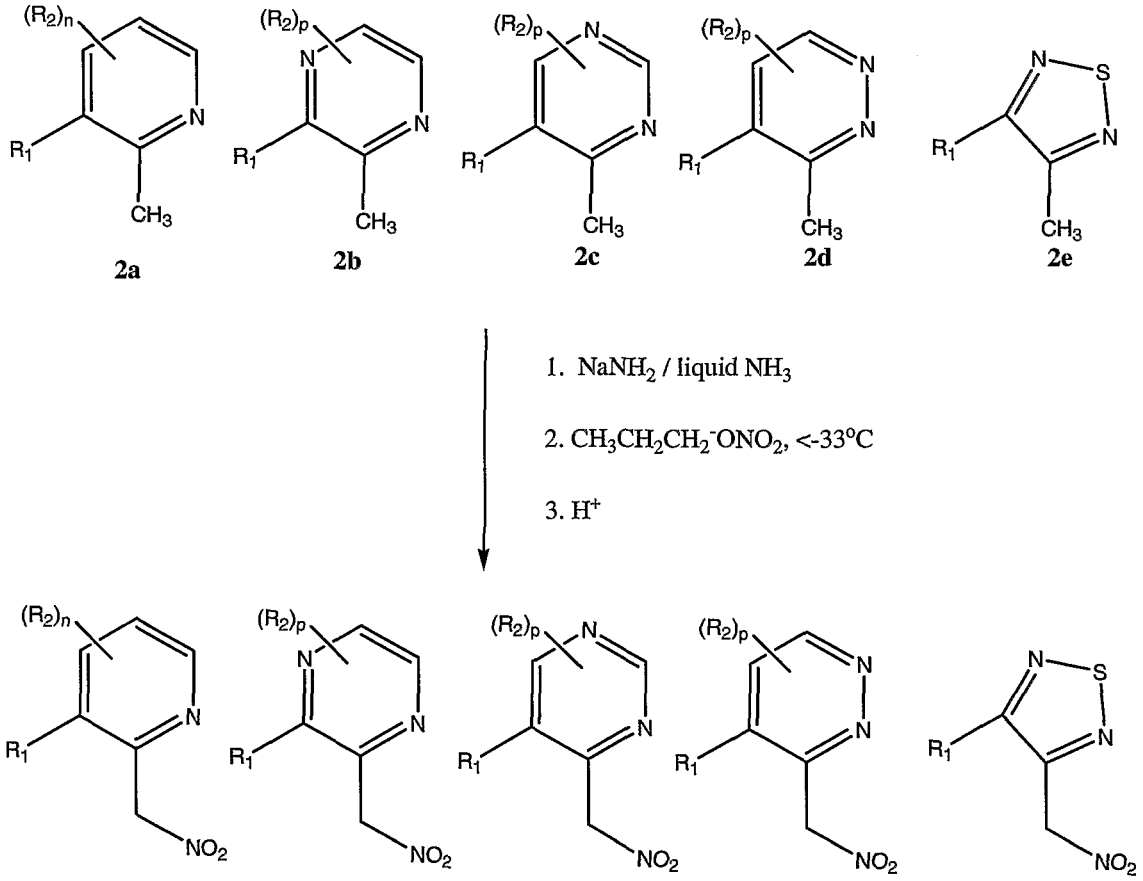
The compounds of formula **16a-e** where Y is $-COOR_{10}$ can be obtained by reacting a compound of formula **16a-e**, where Y is a halogen, with (a) potassium cyanide, (b) water, and (c) $R_{10}OH$ and SO_2Cl according to the procedure described in *Farmaco* 45(9): 945-53 (1990).

The compounds of formula **16a-e** where Y is $-COR_{10}$ can be obtained by reacting a compound of formula **16a-e**, where Y is a halogen, with $R_{10}C(O)H$ and

trimethylsilyl cyanide according to the procedure described in international publication no. WO 01/81333.

The compounds of formula **16a-e** where Y is -CON(R_{13})$_2$ can be obtained by reacting a compound of formula **16a-e**, where Y is a halogen, with (a) potassium cyanide, (b) water, and (c) NH(R_{13})$_2$ and SO_2Cl according to the procedure described in *Farmaco* 45(9): 945-53 (1990

The compounds of formula **16a-e** where Y is -NO_2 can be obtained by by reacting a compound of formula **2a-e** where X is -CH_3 with $NaNH_2$ in liquid NH_3 followed by $CH_3CH_2CH_3$-ONO_2 at a temperature of less than -33°C to provide a nitronate that is then reacted under acidic condition to provide the compound of formula **16a-e** where Y is -NO_2 according to the procedure described by Henry Feuer *et al.*, *J. Am. Chem. Soc.* 91(7) 1856-7 (1969) and as described in the Scheme below:



where R_1, R_2, n and p are defined above for the Piperidine Compounds.

The compounds of formula **16a-e** where Y is -halo are commercially available or can be prepared by methods known to those skilled in the art.

Certain Piperidine Compounds can have one or more asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A Piperidine Compound can be in the form of an optical isomer or a diastereomer. Accordingly, the invention encompasses Piperidine Compounds and their uses as described herein in the form of their optical isomers, diasteriomers, and mixtures thereof, including a racemic mixture. Optical isomers of the Piperidine Compounds can be obtained by known techniques such as chiral chromatography or formation of diastereomeric salts from an optically active acid or base.

In addition, one or more hydrogen, carbon or other atoms of a Piperidine Compound can be replaced by an isotope of the hydrogen, carbon or other atoms. Such compounds, which are encompassed by the present invention, are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

4.7 THERAPEUTIC USES OF THE PIPERIDINE COMPOUNDS

In accordance with the invention, the Piperidine Compounds are administered to an animal in need of treatment or prevention of a Condition.

In one embodiment, an effective amount of a Piperidine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting VR1. Examples of conditions that are treatable or preventable by inhibiting VR1 include, but are not limited to, pain, UI, an ulcer, IBD, and IBS.

In another embodiment, an effective amount of a Piperidine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR5. Examples of conditions that are treatable or preventable by inhibiting mGluR5 include, but are not limited to, pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, and psychosis.

In another embodiment, an effective amount of a Piperidine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR1. Examples of conditions that are treatable or preventable by inhibiting mGluR1 include, but are not limited to, pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, and depression.

The Piperidine Compounds can be used to treat or prevent acute or chronic pain. Examples of pain treatable or preventable using the Piperidine Compounds include, but are not limited to, cancer pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, arthritic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

The Piperidine Compounds can also be used for treating or preventing pain associated with inflammation or with an inflammatory disease in an animal. Such pain can arise where there is an inflammation of the body tissue which can be a local inflammatory response and/or a systemic inflammation. For example, the Piperidine Compounds can be used to treat or prevent pain associated with inflammatory diseases including, but not limited to: organ transplant rejection; reoxygenation injury resulting from organ transplantation (*see* Grupp *et al.*, *J. Mol. Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory diseases of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer s disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin

spot, a candidal infection or necrobiosis lipoidica diabeticorum); immune-complex vasculitis, and systemic lupus erythematosus (SLE); inflammatory diseases of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. The Piperidine Compounds can also be used for inhibiting, treating, or preventing pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, *e.g.*, shock associated with pro-inflammatory cytokines. Such shock can be induced, *e.g.*, by a chemotherapeutic agent that is adminstered as a treatment for cancer.

The Piperidine Compounds can be used to treat or prevent UI. Examples of UI treatable or preventable using the Piperidine Compounds include, but are not limited to, urge incontinence, stress incontinence, overflow incontinence, neurogenic incontinence, and total incontinence.

The Piperidine Compounds can be used to treat or prevent an ulcer. Examples of ulcers treatable or preventable using the Piperidine Compounds include, but are not limited to, a duodenal ulcer, a gastric ulcer, a marginal ulcer, an esophageal ulcer, or a stress ulcer.

The Piperidine Compounds can be used to treat or prevent IBD, including Crohn's disease and ulcerative colitis.

The Piperidine Compounds can be used to treat or prevent IBS. Examples of IBS treatable or preventable using the Piperidine Compounds include, but are not limited to, spastic-colon-type IBS and constipation-predominant IBS.

The Piperidine Compounds can be used to treat or prevent an addictive disorder, including but not limited to, an eating disorder, an impulse-control disorder, an alcohol-related disorder, a nicotine-related disorder, an amphetamine-related disorder, a cannabis-related disorder, a cocaine-related disorder, an hallucinogen-related disorder, an inhalant-related disorders, and an opioid-related disorder, all of which are further sub-classified as listed below.

Eating disorders include, but are not limited to, Bulimia Nervosa, Nonpurging Type; Bulimia Nervosa, Purging Type; Anorexia; and Eating Disorder not otherwise specified (NOS).

Impulse control disorders include, but are not limited to, Intermittent Explosive Disorder, Kleptomania, Pyromania, Pathological Gambling, Trichotillomania, and Impulse Control Disorder not otherwise specified (NOS).

Alcohol-related disorders include, but are not limited to, Alcohol Induced Psychotic Disorder with delusions, Alcohol Abuse, Alcohol Intoxication, Alcohol Withdrawal, Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol Induced Persisting Dementia, Alcohol Induced Persisting Amnestic Disorder, Alcohol Dependence, Alcohol Induced Psychotic Disorder with hallucinations, Alcohol Induced Mood Disorder, Alcohol Induced Anxiety Disorder, Alcohol Induced Sexual Dysfunction, Alcohol Induced Sleep Disorder, and Alcohol Related Disorder not otherwise specified (NOS).

Nicotine-related disorders include, but are not limited to, Nicotine Dependence, Nicotine Withdrawal, and Nicotine Related Disorder not otherwise specified (NOS).

Amphetamine-related disorders include, but are not limited to, Amphetamine Dependence, Amphetamine Abuse, Amphetamine Intoxication, Amphetamine Withdrawal, Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder with delusions, Amphetamine Induced Psychotic Disorders with hallucinations, Amphetamine Induced Mood Disorder, Amphetamine Induced Anxiety Disorder, Amphetamine Induced Sexual Dysfunction, Amphetamine Induced Sleep Disorder, and Amphetamine Related Disorder not otherwise specified (NOS).

Cannabis-related disorders include, but are not limited to, Cannabis Dependence, Cannabis Abuse, Cannabis Intoxication, Cannabis Intoxication Delirium, Cannabis Induced Psychotic Disorder with delusions, Cannabis Induced Psychotic Disorder with hallucinations, Cannabis Induced Anxiety Disorder, and Cannabis Related Disorder not otherwise specified (NOS).

Cocaine-related disorders include, but are not limited to, Cocaine Dependence, Cocaine Abuse, Cocaine Intoxication, Cocaine Withdrawal, Cocaine Intoxication Delirium, Cocaine Induced Psychotic Disorder with delusions, Cocaine Induced Psychotic Disorders with hallucinations, Cocaine Induced Mood Disorder, Cocaine Induced Anxiety Disorder, Cocaine Induced Sexual Dysfunction, Cocaine Induced Sleep Disorder, and Cocaine Related Disorder not otherwise specified (NOS).

Hallucinogen-related disorders include, but are not limited to, Hallucinogen Dependence, Hallucinogen Abuse, Hallucinogen Intoxication,

Hallucinogen Withdrawal, Hallucinogen Intoxication Delirium, Hallucinogen Persisting Perception Disorder (Flashbacks), Hallucinogen Induced Psychotic Disorder with delusions, Hallucinogen Induced Psychotic Disorders with hallucinations, Hallucinogen Induced Mood Disorder, Hallucinogen Induced Anxiety Disorder, Hallucinogen Induced Sexual Dysfunction, Hallucinogen Induced Sleep Disorder, and Hallucinogen Related Disorder not otherwise specified (NOS).

Inhalant-related disorders include, but are not limited to, Inhalant Dependence, Inhalant Abuse, Inhalant Intoxication, Inhalant Intoxication Delirium, Inhalant Induced Psychotic Disorder with delusions, Inhalant Induced Psychotic Disorder with hallucinations, Inhalant Induced Anxiety Disorder, and Inhalant Related Disorder not otherwise specified (NOS).

Opioid-related disorders include, but are not limited to, Opioid Dependence, Opioid Abuse, Opioid Withdrawal, Opioid Intoxication, Opioid Intoxication Delirium, Opioid Induced Psychotic Disorder with delusions, Opioid Induced Psychotic Disorder with hallucinations, Opioid Induced Anxiety Disorder, and Opioid Related Disorder not otherwise specified (NOS).

The Piperidine Compounds can be used to treat or prevent Parkinson's disease and parkinsonism and the symptoms associated with Parkinson's disease and parkinsonism, including but not limited to, bradykinesia, muscular rigidity, resting tremor, and impairment of postural balance.

The Piperidine Compounds can be used to treat or prevent generalized anxiety or severe anxiety and the symptoms associated with anxiety, including but not limited to, restlessness; tension; tachycardia; dyspnea; depression, including chronic "neurotic" depression; panic disorder; agoraphobia and other specific phobias; eating disorders; and personality disorders.

The Piperidine Compounds can be used to treat or prevent epilepsy, including but not limited to, partial epilepsy, generalized epilepsy, and the symptoms associated with epilepsy, including but not limited to, simple partial seizures, jacksonian seizures, complex partial (psychomotor) seizures, convulsive seizures (grand mal or tonic-clonic seizures), petit mal (absence) seizures, and status epilepticus.

The Piperidine Compounds can be used to treat or prevent strokes, including but not limited to, ischemic strokes and hemorrhagic strokes.

The Piperidine Compounds can be used to treat or prevent a seizure, including but not limited to, infantile spasms, febrile seizures, and epileptic seizures.

The Piperidine Compounds can be used to treat or prevent a pruritic condition, including but not limited to, pruritus caused by dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, milaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, or fiberglass dermatitis.

The Piperidine Compounds can be used to treat or prevent psychosis, including but not limited to, schizophrenia, including paranoid schizophrenia, hebephrenic or disorganized schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, negative or deficit subtype schizophrenia, and non-deficit schizophrenia; a delusional disorder, including erotomanic subtype delusional disorder, grandiose subtype delusional disorder, jealous subtype delusional disorder, persecutory subtype delusional disorder, and somatic subtype delusional disorder; and brief psychosis.

The Piperidine Compounds can be used to treat or prevent a cognitive disorder, including but not limited to, delirium and dementia such as multi-infarct dementia, dementia pugilistica, dimentia caused by AIDS, and dementia caused by Alzheimer's disease.

The Piperidine Compounds can be used to treat or prevent a memory deficiency, including but not limited to, dissociative amnesia and dissociative fugue.

The Piperidine Compounds can be used to treat or prevent restricted brain function, including but not limited to, that caused by surgery or an organ transplant, restricted blood supply to the brain, a spinal cord injury, a head injury, hypoxia, cardiac arrest, or hypoglycemia.

The Piperidine Compounds can be used to treat or prevent Huntington's chorea.

The Piperidine Compounds can be used to treat or prevent ALS.

The Piperidine Compounds can be used to treat or prevent retinopathy, including but not limited to, arteriosclerotic retinopathy, diabetic arteriosclerotic retinopathy, hypertensive retinopathy, non-proliferative retinopathy, and proliferative retinopathy.

The Piperidine Compounds can be used to treat or prevent a muscle spasm.

The Piperidine Compounds can be used to treat or prevent a migraine.

The Piperidine Compounds can be used to treat or prevent vomiting, including but not limited to, nausea vomiting, dry vomiting (retching), and regurgitation.

The Piperidine Compounds can be used to treat or prevent dyskinesia, including but not limited to, tardive dyskinesia and biliary dyskinesia.

The Piperidine Compounds can be used to treat or prevent depression, including but not limited to, major depression and bipolar disorder.

Applicants believe that the Piperidine Compounds are antagonists for VR1.

The invention also relates to methods for inhibiting VR1 function in a cell comprising contacting a cell capable of expressing VR1 with an effective amount of a Piperidine Compound. This method can be used *in vitro*, for example, as an assay to select cells that express VR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an ulcer, IBD, or IBS. The method is also useful for inhibiting VR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an effective amount of a Piperidine Compound. In one embodiment, the method is useful for treating or preventing pain in an animal. In another embodiment, the method is useful for treating or preventing UI in an animal. In another embodiment, the method is useful for treating or preventing an ulcer in an animal. In another embodiment, the method is useful for treating or preventing IBD in an animal. In another embodiment, the method is useful for treating or preventing IBS in an animal.

Examples of tissue comprising cells capable of expressing VR1 include, but are not limited to, neuronal, brain, kidney, urothelium, and bladder tissue. Methods for assaying cells that express VR1 are known in the art.

Applicants believe that the Piperidine Compounds are antagonists for mGluR5.

The invention also relates to methods for inhibiting mGluR5 function in a cell comprising contacting a cell capable of expressing mGluR5 with an amount of a Piperidine Compound effective to inhibit mGluR5 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR5 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, or psychosis. The method is also useful for inhibiting mGluR5 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell,

in an animal, with an amount of a Piperidine Compound effective to inhibit mGluR5 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof.

Examples of cells capable of expressing mGluR5 are neuronal and glial cells of the central nervous system, particularly the brain, especially in the nucleus accumbens. Methods for assaying cells that express mGluR5 are known in the art.

Applicants believe that the Piperidine Compounds are antagonists for mGluR1.

The invention also relates to methods for inhibiting mGluR1 function in a cell comprising contacting a cell capable of expressing mGluR1 with an amount of a Piperidine Compound effective to inhibit mGluR1 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression. The method is also useful for inhibiting mGluR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an amount of a Piperidine Compound effective to inhibit mGluR1 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing UI in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing

parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing epilepsy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing stroke in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a seizure in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a cognitive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a memory deficit in an animal in need thereof. In another embodiment, the method is useful for treating or preventing restricted brain function in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Huntington's chorea in an animal in need thereof. In another embodiment, the method is useful for treating or preventing ALS in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dementia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing retinopathy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a muscle spasm in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a migraine in an animal in need thereof. In another embodiment, the method is useful for treating or preventing vomiting in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dyskinesia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing depression in an animal in need thereof.

Examples of cells capable of expressing mGluR1 include, but are not limited to, cerebellar Purkinje neuron cells, Purkinje cell bodies (punctate), cells of spine(s) of the cerebellum; neurons and neurophil cells of olfactory-bulb glomeruli; cells of the superficial layer of the cerebral cortex; hippocampus cells; thalamus cells; superior colliculus cells; and spinal trigeminal nucleus cells. Methods for assaying cells that express mGluR1 are known in the art.

4.8 THERAPEUTIC/PROPHYLACTIC ADMINISTRATION AND COMPOSITIONS OF THE INVENTION

Due to their activity, the Piperidine Compounds are advantageously useful in veterinary and human medicine. As described above, the Piperidine Compounds are useful for treating or preventing a Condition.

When administered to an animal, the Piperidine Compounds are administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The present compositions, which comprise a Piperidine Compound, can be administered orally. The Piperidine Compounds of the invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, *etc.*) and can be administered together with another therapeutically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*, and can be used to administer the Piperidine Compound.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of the Piperidine Compounds into the bloodstream.

In specific embodiments, it can be desirable to administer the Piperidine Compounds locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce the Piperidine Compounds into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a

fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the Piperidine Compounds can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the Piperidine Compounds can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In yet another embodiment, the Piperidine Compounds can be delivered in a controlled-release system or sustained-release system (*see*, *e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the Piperidine Compounds, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal.

Such pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to an animal. Water is a particularly useful excipient when the Piperidine Compound is administered intravenously. Saline solutions and aqueous dextrose and

glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Piperidine Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Piperidine Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the Piperidine Compounds are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the Piperidine Compounds are administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

The Piperidine Compounds can be administered by controlled-release or sustained-release means or by delivery devices that are known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-sustained counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Piperidine Compound to cure or control the condition in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency,

and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Piperidine Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Piperidine Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Piperidine Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Piperidine Compound in the body, the Piperidine Compound can be released from the dosage form at a rate that will replace the amount of Piperidine Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Piperidine Compound that is effective in the treatment or prevention of a condition can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the Condition and can be decided according to the judgment of a practitioner and and/or each animal's circumstances. Suitable effective dosage amounts, however, range from about 0.01 mg/kg of body weight to about 2500 mg/kg of body weight, although they are typically about 100 mg/kg of body weight or less. In one embodiment, the effective dosage amount ranges from about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a Piperidine Compound, in another embodiment, about 0.02 mg/kg of body weight to about 50 mg/kg of body weight, and in another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight. In one embodiment, an effective dosage amount is administered about every 24 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 12 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 8 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 6 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 4 h until the Condition is abated. The effective dosage

amounts described herein refer to total amounts administered; that is, if more than one Piperidine Compound is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing VR1, mGluR5 or mGluR1 is contacted with a Piperidine Compound *in vitro*, the amount effective for inhibiting the VR1, mGluR5 or mGluR1 receptor function in a cell will typically range from about 0.01 μg/L to about 5 mg/L, in one embodiment, from about 0.01 μg/L to about 2.5 mg/L, in another embodiment, from about 0.01 μg/L to about 0.5 mg/L, and in another embodiment, from about 0.01 μg/L to about 0.25 mg/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Piperidine Compound is from about 0.01 μL to about 1 mL. In another embodiment, the volume of solution or suspension is about 200 μL.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Piperidine Compound *in vivo*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 mg/kg of body weight to about 2500 mg/kg of body weight, although it typically ranges from about 100 mg/kg of body weight or less. In one embodiment, the effective dosage amount ranges from about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a Piperidine Compound, in another embodiment, about 0.020 mg/kg of body weight to about 50 mg/kg of body weight, and in another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight. In one embodiment, an effective dosage amount is administered about every 24 h. In another embodiment, an effective dosage amount is administered about every 12 h. In another embodiment, an effective dosage amount is administered about every 8 h. In another embodiment, an effective dosage amount is administered about every 6 h. In another embodiment, an effective dosage amount is administered about every 4 h.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Piperidine Compound *in vitro*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 μg/L to about 5 mg/L, in one embodiment, from about 0.01 μg/L to about 2.5 mg/L, in another embodiment, from about 0.01 μg/L to about 0.5 mg/L, and in another embodiment, from about 0.01 μg/L to about 0.25 mg/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension is from about 1 μL

to about 1 mL. In another embodiment, the volume of solution or suspension is about 200 μL.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Piperidine Compound *in vivo*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 mg to about 100 mg/kg of body weight per day, in one embodiment, from about 0.1 mg to about 50 mg/kg body weight per day, and in another embodiment, from about 1 mg to about 20 mg/kg of body weight per day.

The Piperidine Compounds can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The present methods for treating or preventing a Condition in an animal in need thereof can further comprise administering to the animal being administered a Piperidine Compound another therapeutic agent. In one embodiment, the other therapeutic agent is administered in an effective amount.

The present methods for inhibiting VR1 function in a cell capable of expressing VR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR5 function in a cell capable of expressing mGluR5 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR1 function in a cell capable of expressing mGluR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

Effective amounts of the other therapeutic agents are known to those skilled in the art. However, it is within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the invention, where another therapeutic agent is administered to an animal, the effective amount of the Piperidine Compound is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the Piperidine Compounds and the other therapeutic agent act synergistically to treat or prevent a Condition.

The other therapeutic agent can be, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroid anti-inflammatory agent, an antimigraine agent, a

Cox-II inhibitor, an antiemetic, a β-adrenergic blocker, an anticonvulsant, an antidepressant, a Ca2+-channel blocker, an anticancer agent, an agent for treating or preventing UI, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating addictive disorder, an agent for treating Parkinson's disease and parkinsonism, an agent for treating anxiety, an agent for treating epilepsy, an agent for treating a stroke, an agent for treating a seizure, an agent for treating a pruritic condition, an agent for treating psychosis, an agent for treating Huntington's chorea, an agent for treating ALS, an agent for treating a cognitive disorder, an agent for treating a migraine, an agent for treating vomiting, an agent for treating dyskinesia, or an agent for treating depression, and mixtures thereof.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

Examples of useful non-opioid analgesics include non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid,

meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophennol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs, *see Paul A. Insel, Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9th ed. 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed., 19th ed. 1995) which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, rofecoxib and celecoxib.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, bromocriptine, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergonovine, ergot, ergotamine, flumedroxone acetate, fonazine, ketanserin, lisuride, lomerizine, methylergonovine, methysergide, metoprolol, naratriptan, oxetorone, pizotyline, propranolol, risperidone, rizatriptan, sumatriptan, timolol, trazodone, zolmitriptan, and mixtures thereof.

The other therapeutic agent can also be an agent useful for reducing any potential side effects of a Piperidine Compound. For example, the other therapeutic agent can be an antiemetic agent. Examples of useful antiemetic agents include, but are not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine,

acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

Examples of useful β-adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulabol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

Examples of useful antidepressants include, but are not limited to, binedaline, caroxazone, citalopram, (S)-citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrocholoride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole,

lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflozane, piberaline, prolintane, pyrisuccideanol, ritanserin, roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

Examples of useful Ca2+-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, and perhexiline.

Examples of useful anticancer agents include, but are not limited to, acivicin, aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, edatrexate, eflornithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, etoposide, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine hydrochloride, hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofosine, interleukin II (including recombinant interleukin II or rIL2), interferon alpha-2a, interferon alpha-2b, interferon alpha-n1, interferon

alpha-n3, interferon beta-I a, interferon gamma-I b, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, maytansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedepa, mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitosper, mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole, nogalamycin, ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin sulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, riboprine, rogletimide, safingol, safingol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, sulofenur, talisomycin, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, teniposide, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, toremifene citrate, trestolone acetate, triciribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine sulfate, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinate sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, zorubicin hydrochloride.

Examples of other anti-cancer drugs include, but are not limited to, 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine;

budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dihydrotaxol; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; 4-ipomeanol; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene;

molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline;

thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, and dicyclomine.

Examples of useful therapeutic agents for treating or preventing an ulcer include, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate; sucraflate; bismuth compounds such as bismuth subsalicylate and bismuth subcitrate; H_2 antagonists such as cimetidine, ranitidine, famotidine, and nizatidine; H^+, K^+ - ATPase inhibitors such as omeprazole, iansoprazole, and lansoprazole; carbenoxolone; misprostol; and antibiotics such as tetracycline, metronidazole, timidazole, clarithromycin, and amoxicillin.

Examples of useful therapeutic agents for treating or preventing IBD include, but are not limited to, anticholinergic drugs; diphenoxylate; loperamide; deodorized opium tincture; codeine; broad-spectrum antibiotics such as metronidazole; sulfasalazine; olsalazie; mesalamine; prednisone; azathioprine; mercaptopurine; and methotrexate.

Examples of useful therapeutic agents for treating or preventing IBS include, but are not limited to, propantheline; muscarine receptor antogonists such as pirenzapine, methoctramine, ipratropium, tiotropium, scopolamine, methscopolamine, homatropine, homatropine methylbromide, and methantheline; and antidiarrheal drugs such as diphenoxylate and loperamide.

Examples of useful therapeutic agents for treating or preventing an addictive disorder include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, levomethadyl acetate hydrochloride, and serotonin antagonists.

Examples of useful therapeutic agents for treating or preventing Parkinson's disease and parkinsonism include, but are not limited to, carbidopa/levodopa, pergolide, bromocriptine, ropinirole, pramipexole, entacapone, tolcapone, selegiline, amantadine, and trihexyphenidyl hydrochloride.

Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsaprione, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; and propanediol carbamates, such as meprobamate and tybamate.

Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, gabapentin, lamotrigine, γ-vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing stroke include, but are not limited to, anticoagulants such as heparin, agents that break up clots such as streptokinase or tissue plasminogen activator, agents that reduce swelling such as mannitol or corticosteroids, and acetylsalicylic acid.

Examples of useful therapeutic agents for treating or preventing a seizure include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, gabapentin, lamotrigine, γ-vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing a pruritic condition include, but are not limited to, naltrexone; nalmefene; danazol; tricyclics such as amitriptyline, imipramine, and doxepin; antidepressants such as those given below, menthol; camphor; phenol; pramoxine; capsaicin; tar; steroids; and antihistamines.

Examples of useful therapeutic agents for treating or preventing psychosis include, but are not limited to, phenothiazines such as chlorpromazine hydrochloride, mesoridazine besylate, and thoridazine hydrochloride; thioxanthenes such as chloroprothixene and thiothixene hydrochloride; clozapine; risperidone; olanzapine;

quetiapine; quetiapine fumarate; haloperidol; haloperidol decanoate; loxapine succinate; molindone hydrochloride; pimozide; and ziprasidone.

Examples of useful therapeutic agents for treating or preventing Huntington's chorea include, but are not limited to, haloperidol and pimozide.

Examples of useful therapeutic agents for treating or preventing ALS include, but are not limited to, baclofen, neurotrophic factors, riluzole, tizanidine, benzodiazepines such as clonazepan and dantrolene.

Examples of useful therapeutic agents for treating or preventing cognitive disorders include, but are not limited to, agents for treating or preventing dementia such as tacrine; donepezil; ibuprofen; antipsychotic drugs such as thioridazine and haloperidol; and antidepressant drugs such as those given below.

Examples of useful therapeutic agents for treating or preventing a migraine include, but are not limited to, sumatriptan; methysergide; ergotamine; caffeine; and beta-blockers such as propranolol, verapamil, and divalproex.

Examples of useful therapeutic agents for treating or preventing vomiting include, but are not limited to, 5-HT_3 receptor antagonists such as ondansetron, dolasetron, granisetron, and tropisetron; dopamine receptor antagonists such as prochlorperazine, thiethylperazine, chlorpromazin, metoclopramide, and domperidone; glucocorticoids such as dexamethasone; and benzodiazepines such as lorazepam and alprazolam.

Examples of useful therapeutic agents for treating or preventing dyskinesia include, but are not limited to, reserpine and tetrabenazine.

Examples of useful therapeutic agents for treating or preventing depression include, but are not limited to, tricyclic antidepressants such as amitryptyline, amoxapine, bupropion, clomipramine, desipramine, doxepin, imipramine, maprotilinr, nefazadone, nortriptyline, protriptyline, trazodone, trimipramine, and venlaflaxine; selective serotonin reuptake inhibitors such as citalopram, (S)-citalopram, fluoxetine, fluvoxamine, paroxetine, and setraline; monoamine oxidase inhibitors such as isocarboxazid, pargyline, phenelzine, and tranylcypromine; and psychostimulants such as dextroamphetamine and methylphenidate.

A Piperidine Compound and the other therapeutic agent can act additively or, in one embodiment, synergistically. In one embodiment, a Piperidine Compound is administered concurrently with another therapeutic agent; for example, a composition comprising an effective amount of a Piperidine Compound and an effective amount of

another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a Piperidine Compound and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a Piperidine Compound is administered prior or subsequent to administration of an effective amount of another therapeutic agent. In this embodiment, the Piperidine Compound is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Piperidine Compound exerts its therapeutic effect for treating or preventing a Condition.

A composition of the invention is prepared by a method comprising admixing a Piperidine Compound or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods known for admixing a compound (or salt) and a pharmaceutically acceptable carrier or excipient. In one embodiment the Piperidine Compound is present in the composition in an effective amount.

4.9 KITS

The invention encompasses kits that can simplify the administration of a Piperidine Compound to an animal.

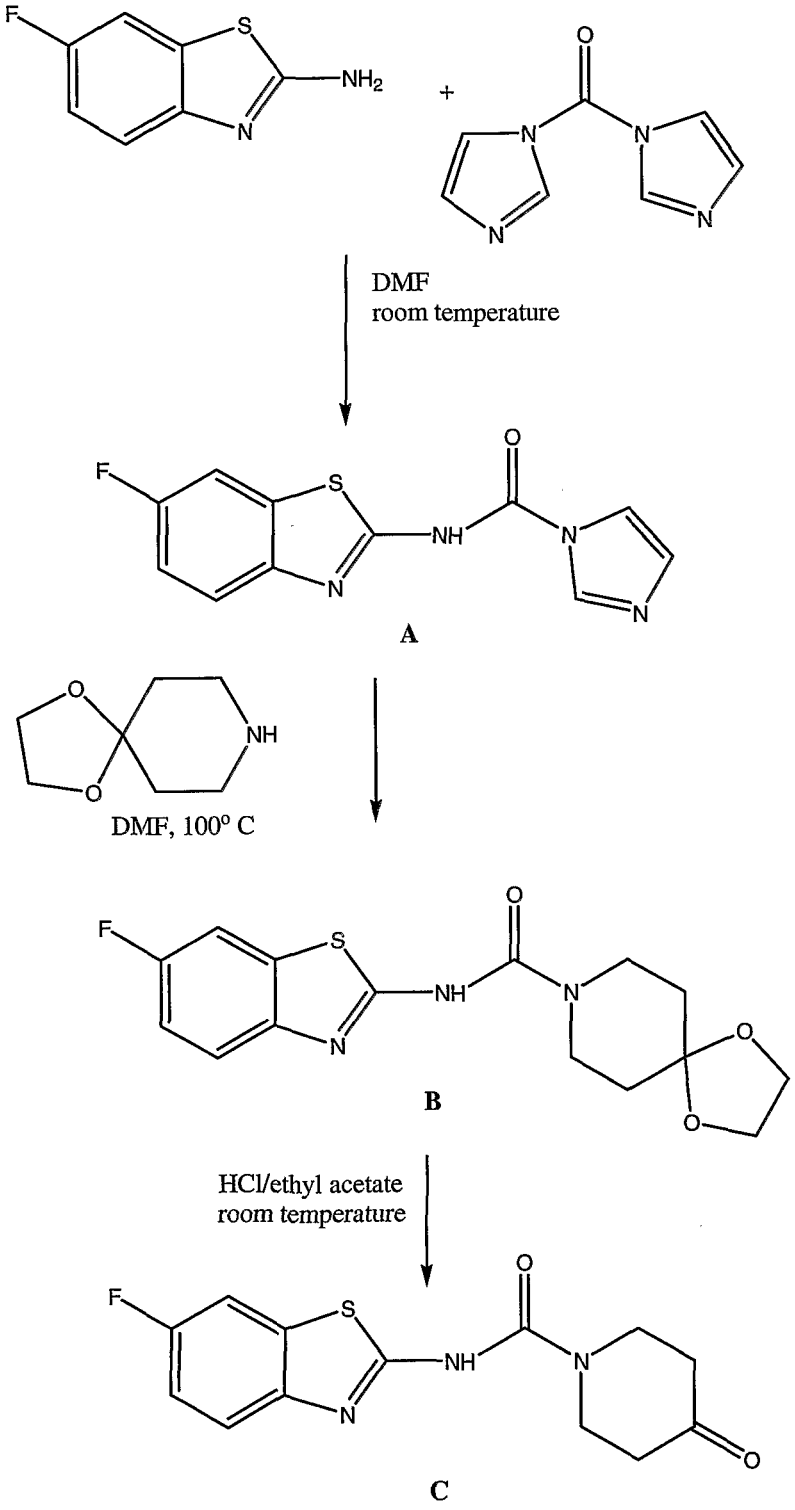
A typical kit of the invention comprises a unit dosage form of a Piperidine Compound. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Piperidine Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Piperidine Compound to treat a Condition. The kit can also further comprise a unit dosage form of another therapeutic agent, for example, a second container containing an effective amount of the other therapeutic agent and a pharmaceutically acceptable carrier or excipient. In another embodiment, the kit comprises a container containing an effective amount of a Piperidine Compound, an effective amount of another therapeutic agent and a pharmaceutically acceptable carrier or excipient. Examples of other therapeutic agents include, but are not limited to, those listed above.

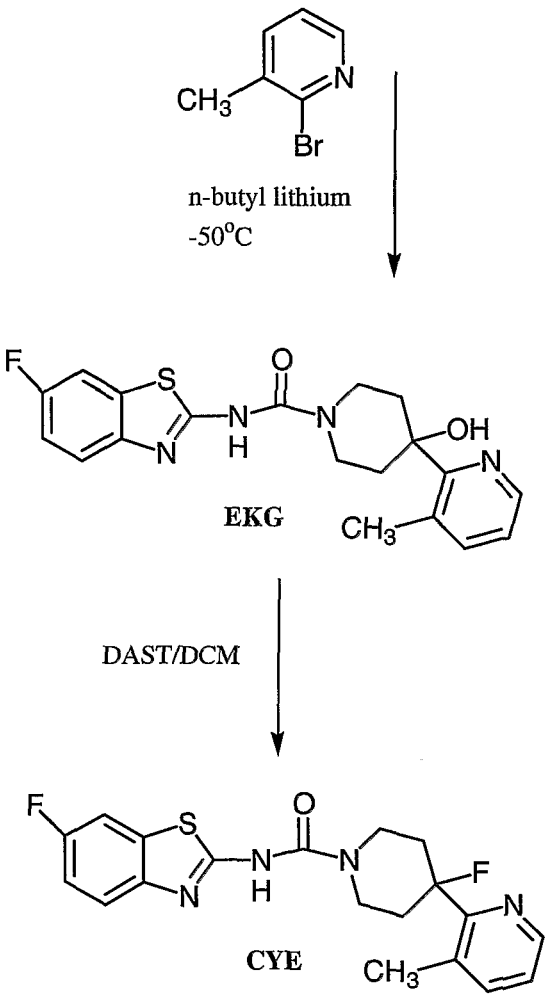
Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device include, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

5. EXAMPLES

5.1 EXAMPLE 1: SYNTHESIS OF PIPERIDINE COMPOUNDS CYE AND EKG





2-amino-6-fluorobenzothiazole (15.0 g, 89.2 mmol) was dissolved in DMF (100 mL) and cooled to about 0°C under a nitrogen atmosphere. 1,1-Carbonyldiimidazole (15.2g, 93.6 mmol) was added to the reaction mixture and the reaction mixture allowed to stir at about 0°C for about 1 h. The reaction mixture was then allowed to warm to about 25°C and stirred for about 3 h. The resulting reaction mixture was then diluted with acetone (100 mL) and filtered to provide the acyl-imidaxole **A** (14.5 g, 55.2 mmol) as a yellowish solid. The acyl-imidaxole **A** was *suspended in anhydrous DMF (100 mL), 1,4-dioxa-8-aza-spiro [4,5] decane (7.9g, 55.2* mmol) was added to the resulting suspension, and the suspension was allowed to stir for about 1 h. at about 100°C under a nitrogen atmosphere. The solvent was then removed under reduced pressure and the resulting residue poured into a 1M aqueous sodium bicarbonate solution and allowed to stir for about 1 h. The reaction mixture was then filtered and the filtrate dried under vacuum. The resulting solid was washed with diethyl ether (150 mL) to provide Compound **B** as a yellowish solid (19.0 g, 65% yield).

Compound **B** (19.0 g) was suspended in a mixture of ethyl acetate (150 mL) and hydrochloric acid (50 mL) and heated under reflux for about 4 h. The resulting reaction mixture was then cooled to about 25°C, poured into water (400 mL) and the pH of the resulting solution adjusted to a value of above 10 using aqueous potassium carbonate. The resulting solution was then extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and removed under reduced pressure to provide a solid that was washed with diethyl ether to provide the Compound of formula **C** as a light yellow solid (12.0g, 82% yield).

To a solution of n-butyl lithium (1.6M in hexane, 6.31 mL, 10.24 mmol) in diethyl ether (5 mL) was added drop-wise a solution of 2-bromo-3-methylpyridine (1.76 g, 10.24 mmol) in anhydrous ethyl ether (95 mL) at about -78°C under a nitrogen atmosphere. The resulting solution was allowed to warm up to about -50°C and stirred for about 1 h. The compound of formula **C** (1 g, 3.41 mmol), dissolved in THF (15 mL), was then added drop-wise to the resulting mixture and the mixture stirred for about 1 h. at -50°C. The resulting reaction mixture was then quenched with saturated aqueous ammonium chloride at about 0°C and the resulting mixture extracted with diethyl ether. The ether layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford a solid that was purified using flash chromatography (silica gel eluted with a gradient elution from 30:70 ethyl acetate:hexane to 70:30 ethyl acetate:hexane) to provide Compound **EKG** as a white solid.

To a suspension of Compound **EKG** (0.74 g, 1.92 mmol) in DCM (10 mL) was added drop-wise a solution of DAST (0.62 g, 3.84 mmol) at about -78°C under a nitrogen atmosphere. The resulting mixture was allowed to warm to about -50°C and stirred at about -50°C for about 2 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with DCM. The DCM was dried (Na_2SO_4) and the DCM removed under reduced pressure to provide a solid that was purified using a silica column eluted with 30:70 ethyl acetate:hexane to afford Compound **CYE** as a white solid.

The Structure of Compounds **B**, **C**, **EKG**, and **CYE** was confirmed by ^1H NMR.

Compound **B**: ^1H NMR ($CDCl_3$) δ 9.67 (br s, 1H), 756 (s, 1H), 7.44 (br, s, 1H), 7.23 (d, J=7.9 Hz, 1H), 3.97 (m. 4H), 2.58 (t, J=6.2 Hz, 4H), 2.49 (m, 4H) ppm.

Compound **C**: ^1H NMR ($CDCl_3$) δ 9.44 (br s, 1H), 7.57 (m, 1H), 7.51 (d, J=6.6 Hz, 1H), 7.17 (m, 1H), 3.95 (t, J=6.0 Hz, 4H), 2.61 (t, J=6.0 Hz, 4H) ppm.

Compound **EKG**: ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J=4.5 Hz, 1H), 7.78 (dd, J=4.5, 8.7 Hz, 1H), 7.45 (m, 2H), 7.16 (dd, J=8.7, 11.6 Hz, 1H), 7.10 (m, 1H), 6.68 (br s, 1H), 4.16 (m, 1H), 3.58 (t, J=12.4 Hz, 2H), 2.47 (s, 3H), 2.42 (m, 3H), 1.50 (d, J=12.4 Hz, 2H) ppm.

Compound **CYE**: ^{1}H NMR ($CDCl_3$) δ 10.40 (br s 1H), 8.32 (d, J=4.5 Hz, 1H), 7.47 (d, J=7.7 Hz, 2H), 7.13 (m, 2H), 4.41 (d, J=12.0, Hz, 2H), 3.44 (t, J=12.4 Hz, 2H), 2.47 (s, 3H), 2.36 (m, 3H), 2.07 (t, J=12.4 Hz, 2H) ppm.

5.2 EXAMPLE 2: SYNTHESIS OF PIPERIDINE COMPOUNDS AYH AND AMT

Compounds **AYH** and **AMT** were obtained by a method analogous to that used to obtain Compounds **EKG** and **CYE** as described above in Example 1 except that 4-*tert*-butyl aniline was used in place of 2-amino-6-fluorobenzothiazole.

5.3 EXAMPLE 3: SYNTHESIS OF PIPERIDINE COMPOUNDS EKE AND CYC

Compounds **EKE** and **CYC** were obtained by methods analogous to those described above.

The Structure of Compounds **EKE** and **CYC** was confirmed by ^{1}H NMR and mass spectrometry (MS).

Compound **EKE**: ^{1}H NMR ($CDCl_3$) δ 8.40 (dd, J=1.0, 4.7 Hz, 1H), 7.77 (d, J=2.0 Hz, 1H), 7.59 (d, J=8.6 Hz, 1H), 7.55 (dd, J=0.8, 7.6 Hz, 1H), 7.36 (dd, J=2.0, 8.6 Hz, 1H), 7.22 (dd, J=4.7, 7.6 Hz, 1H), 6.75 (br s, 1H), 4.20 (m, 2H), 3.64 (t, J=12.2 Hz, 2H), 2.50 (s, 3H), 2.40 (dt, J=4.9, 13.1 Hz, 2H), 1.73 (br s, 1H), 1.58 (d, J=12.7 Hz, 2H) ppm.

MS: 403.2 m/z (m+1).

Compound **CYC**: ^{1}H NMR ($CDCl_3$) δ 9.24 (br s, 1H), 8.36 (d, J=4.6 Hz, 1H), 7.77 (d, J=2.0 Hz, 1H), 7.56 (d, J=8.6 Hz, 1H), 7.50 (d, J=7.6 Hz, 1H), 7.37 (dd, J=2.0, 8.6 Hz, 1H), 7.15 (dd, J=4.7, 7.6 Hz, 1H), 4.15 (m, 2H), 3.48 (t, J=12.7 Hz, 2H), 2.52 (d, J=5.9 Hz, 3H), 2.17 (dt, J=1.6, 9.9 Hz, 2H), 1.67 (m, 2H) ppm.

MS: 405.1 m/z (m+1).

5.4 EXAMPLE 4: BINDING OF PIPERIDINE COMPOUNDS TO mGluR5

The following assay can be used to demonstrate that Piperidine Compounds bind to mGluR5 and, accordingly, are useful for treating or preventing, *e.g.*, pain.

Cell cultures: Primary glial cultures are prepared from cortices of Sprague-Dawley 18 days old embryos. The cortices are dissected and then dissociated by trituration. The resulting cell homogenate is plated onto poly-D-lysine precoated T175 flasks (BIOCOAT, commercially available from Becton Dickinson and Company, Inc. of Franklin Lakes, NJ) in Dulbecco's Modified Eagle's Medium ("DMEM," pH 7.4), buffered with 25 mM HEPES, and supplemented with 15% fetal calf serum ("FCS," commercially available from Hyclone Laboratories Inc. of Omaha, NE), and incubated at 37°C and 5% CO_2. After 24 hours, FCS supplementation is reduced to 10%. On day six, oligodendrocytes and microglia are removed by strongly tapping the sides of the flasks. One day following this purification step, secondary astrocyte cultures are established by subplating onto 96 poly-D-lysine precoated T175 flasks (BIOCOAT) at a density of 65,000 cells/well in DMEM and 10% FCS. After 24 hours, the astrocytes are washed with serum free medium and then cultured in DMEM, without glutamate, supplemented with 0.5% FCS, 20 mM HEPES, 10 ng/mL epidermal growth factor ("EGF"), 1 mM sodium pyruvate, and 1X penicillin/streptomycin at pH 7.5 for 3 to 5 days at 37°C and 5% CO_2. The procedure allows the expression of the mGluR5 receptor by astrocytes, as demonstrated by S. Miller *et al.*, *J. Neuroscience* 15(9):6103-6109 (1995).

Assay Protocol: After 3-5 days incubation with EGF, the astrocytes are washed with 127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 700 mM NaH_2PO_4, 2 mM $CaCl_2$, 5 mM $NaHCO_3$, 8 mM HEPES, 10 mM Glucose at pH 7.4 ("Assay Buffer") and loaded with the dye Fluo-4 (commercially available from Molecular Probes Inc. of Eugene, OR) using 0.1 mL of Assay Buffer containing Fluo-4 (3 mM final). After 90 minutes of dye loading, the cells are then washed twice with 0.2 mL Assay Buffer and resuspended in 0.1 mL of Assay Buffer. The plates containing the astrocytes are then transferred to a Fluorometric Imaging Plate reader ("FLIPR," commercially available from Molecular Devices Corporation of Sunnyvale, CA) for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of antagonist. After monitoring fluorescence for 15 seconds to establish a baseline, DMSO solutions

containing various concentrations of a Piperidine Compound diluted in Assay Buffer (0.05 mL of 4X dilutions for competition curves) are added to the cell plate and fluorescence is monitored for 2 minutes. 0.05 mL of a 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 mM. Plate fluorescence is then monitored for an additional 60 seconds after agonist addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using a non-linear regression to determine the IC_{50} value. In each experiment, each data point is determined two times.

Alternatively, the following assay can be used to demonstrate that Piperadine Compounds bind to mGluR5.

40,000 CHO-rat mGluR5 cells/well are plated into 96 well plate (Costar 3409, Black, clear bottom, 96 well, tissue culture treated) for an overnight incubation in Dulbecco's Modified Eagle's Medium (DMEM, pH 7.4) and supplemented with glutamine, 10% FBS, 1% Pen/Strep, and 500ug/mL Geneticin. CHO-rat mGluR5 cells are washed and treated with Optimem medium and incubated for 1-4 hours prior to loading cells. Cell plates are then washed with loading buffer (127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 700 μM Na H_2PO_4, 2 mM $CaCl_2$, 5 mM $NaHCO_3$, 8 mM Hepes, and 10 mM glucose, pH 7.4) and then incubated with 3μM Fluo 4 (commercially available from Molecular probes Inc. of Eugene, OR) in 0.1 mL of loading buffer. After 90 minutes of dye loading, the cells are then washed twice with 0.2 mL loading buffer and resuspended in 0.1 mL loading buffer.

The plates containing the CHO-rat mGluR5 cells are then transferred to a FLIPR for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of test compounds. After monitoring fluorescence for 15 seconds to establish a baseline, DMSO solutions containing various concentrations of the test compound diluted in loading buffer (0.05 mL of 4X dilutions for the competition curves) are added to the cell plate and fluorescence is monitored for 2 minutes. 0.05 mL of 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 uM. Plate fluorescence is then monitored for an additional 60 seconds after agonist addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using

a non-linear regression to determine the IC_{50} value. In each experiment, each data point is determined two times.

5.5 EXAMPLE 5: IN VIVO ASSAYS FOR PREVENTION OR TREATMENT OF PAIN

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Piperidine Compound when food is removed for 16 hours before dosing. A control group acts as a comparison to rats treated with a Piperidine Compound. The control group is administered the carrier for the Piperidine Compound. The volume of carrier administered to the control group is the same as the volume of carrier and Piperidine Compound administered to the test group.

Acute Pain: To assess the actions of the Piperidine Compounds for the treatment or prevention of acute pain the rat tail flick test can be used. Rats are gently restrained by hand and the tail exposed to a focused beam of radiant heat at a point 5 cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 20 seconds are removed from the tail flick unit and assigned a withdrawal latency of 20 seconds. Tail flick latencies are measured immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Piperidine Compound. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 20 seconds, is calculated as follows:

$$\%\ \text{MPE} = \frac{[\ (\text{post administration latency}) - (\text{pre-administration latency})\ ]}{(20\ \text{s pre-administration latency})} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941).

Acute pain can also be assessed by measuring the animal's response to noxious mechanical stimuli by determining the paw withdrawal threshold ("PWT"), as described below.

Inflammatory Pain: To assess the actions of the Piperidine Compounds for the treatment or prevention of inflammatory pain the Freund's complete adjuvant ("FCA") model of inflammatory pain is used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Capsaicin-sensitive Neurones in Hyperalgesia and Enhanced Opioid Antinociception in Inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacol.* 342:666-670 (1990)). The left hind paw of each animal is administered a 50 μL intraplantar injection of 50% FCA. 24 hour post injection, the animal is assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats are then administered a single injection of 1, 3, 10 or 30 mg/Kg of either a Piperidine Compound; 30 mg/Kg of a control selected from Celebrex, indomethacin or naproxen; or carrier. Responses to noxious mechanical stimuli are then determined 1, 3, 5 and 24 hours post administration. Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT)} - \text{(pre-administration PWT)}]}{[\text{(baseline PWT)} - \text{(pre-administration PWT)}]} \times 100$$

Neuropathic Pain: To assess the actions of the Piperidine Compounds for the treatment or prevention of neuropathic pain either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to ½ of the nerve thickness is held within the ligature. The wound

is closed with a single muscle suture (4-0 nylon (Vicryl)) and vetbond tissue glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration for rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT)} - \text{(pre-administration PWT)}]}{[\text{(baseline PWT)} - \text{(pre-administration PWT)}]} \times 100$$

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anaesthesia a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L_4 - S_2 levels. The L_6 transverse process is carefully removed with a pair of small rongeurs to identify visually the L_4 - L_6 spinal nerves. The left L_5 (or L_5 and L_6) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then be returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a Piperidine Compound for the left rear paw of the animal. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model

for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992).

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia: The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacol. Biochem. and Behavior* 31:451-455 (1988). The maximum weight that can be applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and only the affected (ipsilateral) paw is tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain* 32(1):77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged. Only the affected (ipsilateral) paw is tested.

Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

5.6 EXAMPLE 6: IN VIVO ASSAYS FOR PREVENTION OR TREATMENT OF ANXIETY

The elevated plus maze test or the shock-probe burying test can be used to assess the anxiolytic activity of Piperidine Compounds in rats or mice.

The Elevated Plus Maze Test: The elevated plus maze consists of a platform with 4 arms, two open and two closed (50x10x50 cm enclosed with an open roof). Rats (or mice) are placed in the center of the platform, at the crossroad of the 4 arms, facing one of the closed arms. Time spent in the open arms vs. the closed arms and number of open arm entries during the testing period are recorded. This test is conducted prior to drug administration and again after drug administration. Test results are expressed as the mean time spent in open arms and the mean number of entries into open arms. Known anxiolytic drugs increase both the time spent in open arms and number of open arm entries. The elevated plus maze test is described in D. Treit, "Animal Models for the Study of Anti-anxiety Agents: A Review," *Neuroscience & Biobehavioral Reviews* 9(2):203-222 (1985).

The Shock-Probe Burying Test: For the shock-probe burying test the testing apparatus consists of a plexiglass box measuring 40x30x40 cm, evenly covered with approximately 5 cm of bedding material (odor absorbent kitty litter) with a small hole in one end through which a shock probe (6.5 cm long and 0.5 cm in diameter) is inserted. The plexiglass shock probe is helically wrapped with two copper wires through which an electric current is administered. The current is set at 2 mA. Rats are habituated to the testing apparatus for 30 min on 4 consecutive days without the shock probe in the box. On test day, rats are placed in one corner of the test chamber following drug administration. The probe is not electrified until the rat touches it with its snout or fore paws, at which point the rat receives a brief 2 mA shock. The 15 min testing period begins once the rat receives its first shock and the probe remains electrified for the remainder of the testing period. The shock elicits burying behavior by the rat. Following the first shock, the duration of time the rat spends spraying bedding material toward or over the probe with its snout or fore paws (burying behavior) is measured as well as the number of contact-induced shocks the rat receives from the probe. Known anxiolytic drugs reduce the amount of burying behavior. In addition, an index of the rat's reactivity to each shock is scored on a 4 point scale. The total time spent immobile during the 15 min testing period is used as an index of general activity. The shock-probe burying test is described in D. Treit, 1985, *supra.*

5.7 EXAMPLE 7: *IN VIVO* ASSAYS FOR PREVENTION OR TREATMENT OF AN ADDICTIVE DISORDER

The conditioned place preference test or drug self-administration test can be used to assess the ability of Piperidine Compounds to attenuate the rewarding properties of known drugs of abuse.

The Conditioned Place Preference Test: The apparatus for the conditioned place preference test consists of two large compartments (45 x 45 x 30 cm) made of wood with a plexiglass front wall. These two large compartments are distinctly different. Doors at the back of each large compartment lead to a smaller box (36 x 18 x 20 cm) box made of wood, painted grey, with a ceiling of wire mesh. The two large compartments differ in terms of shading (white vs black), level of illumination (the plexiglass door of the white compartment is covered with aluminum foil except for a window of 7 x 7 cm), texture (the white compartment has a 3 cm thick floor board (40 x 40 cm) with nine equally spaced 5 cm diameter holes and the black has a wire mesh floor), and olfactory cues (saline in the white compartment and 1 mL of 10% acetic acid in the black compartment). On habituation and testing days, the doors to the small box remain open, giving the rat free access to both large compartments.

The first session that a rat is placed in the apparatus is a habituation session and entrances to the smaller grey compartment remain open giving the rat free access to both large compartments. During habituation, rats generally show no preference for either compartment. Following habituation, rats are given 6 conditioning sessions. Rats are divided into 4 groups: carrier pre-treatment + carrier (control group), Piperidine Compound pre-treatment + carrier, carrier pre-treatment + morphine, Piperidine Compound pre-treatment + morphine. During each conditioning session the rat is injected with one of the drug combinations and confined to one compartment for 30 min. On the following day, the rat receives a carrier + carrier treatment and is confined to the other large compartment. Each rat receives three conditioning sessions consisting of 3 drug combination-compartment and 3 carrier-compartment pairings. The order of injections and the drug/compartment pairings are counterbalanced within groups. On the test day, rats are injected prior to testing (30 min to 1 hour) with either morphine or carrier and the rat is placed in the apparatus, the doors to the grey compartment remain open and the rat is allowed to explore the entire apparatus for 20 min. The time spent in each compartment is recorded. Known drugs of abuse increase the time spent in the drug-paired compartment during the testing session. If the Piperidine Compound blocks

the acquisition of morphine conditioned place preference (reward), there will be no difference in time spent in each side in rats pre-treated with a Piperidine Compound and the group will not be different from the group of rats that was given carrier + carrier in both compartments. Data will be analyzed as time spent in each compartment (drug combination-paired vs carrier-paired). Generally, the experiment is repeated with a minimum of 3 doses of a Piperidine Compound.

The Drug Self-Administration Test: The apparatus for the drug self-administration test is a standard commercially available operant conditioning chamber. Before drug trials begin rats are trained to press a lever for a food reward. After stable lever pressing behavior is acquired, rats are tested for acquisition of lever pressing for drug reward. Rats are implanted with chronically indwelling jugular catheters for i.v. administration of compounds and are allowed to recover for 7 days before training begins. Experimental sessions are conducted daily for 5 days in 3 hour sessions. Rats are trained to self-administer a known drug of abuse, such as morphine. Rats are then presented with two levers, an "active" lever and an "inactive" lever. Pressing of the active lever results in drug infusion on a fixed ratio 1 (FR1) schedule (*i.e.*, one lever press gives an infusion) followed by a 20 second time out period (signaled by illumination of a light above the levers). Pressing of the inactive lever results in infusion of excipient. Training continues until the total number of morphine infusions stabilizes to within ± 10% per session. Trained rats are then used to evaluate the effect of Piperidine Compounds pre-treatment on drug self-administration. On test day, rats are pre-treated with a Piperidine Compound or excipient and then are allowed to self-administer drug as usual. If the Piperidine Compound blocks the rewarding effects of morphine, rats pre-treated with the Piperidine Compound will show a lower rate of responding compared to their previous rate of responding and compared to excipient pre-treated rats. Data is analyzed as the change in number of drug infusions per testing session (number of infusions during test session – number of infusions during training session).

5.8 EXAMPLE 8: FUNCTIONAL ASSAY FOR CHARACTERIZING mGluR1 ANTAGONISTIC PROPERTIES

Functional assays for the characterization of mGluR 1 antagonistic properties are known in the art. For example, the following procedure can be used.

A CHO-rat mGluR1 cell line is generated using cDNA encoding rat mGluR1 receptor (M. Masu and S. Nakanishi, *Nature* 349:760-765 (1991)). The cDNA encoding rat mGluR1 receptor can be obtained from, *e.g.*, Prof. S. Nakanishi (Kyoto, Japan).

40,000 CHO-rat mGluR1 cells/well are plated into a COSTAR 3409, black, clear bottom, 96 well, tissue culture treated plate (commercially available from Fisher Scientific of Chicago, IL) and are incubated in Dulbecco's Modified Eagle's Medium (DMEM, pH 7.4) supplemented with glutamine, 10% FBS, 1% Pen/Strep, and 500 μg/mL Geneticin for about 12 h. The CHO-rat mGluR1 cells are then washed and treated with OPTIMEM medium (commercially available from Invitrogen, Carlsbad, CA) and incubated for a time period ranging from 1 to 4 hours prior to loading the cells with the dye FLUO-4 (commercially available from Molecular Probes Inc., Eugene, OR). After incubation, the cell plates are washed with loading buffer (127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 700 μM, NaH_2PO_4, 2 mM $CaCl_2$, 5 mM$NaHCO_3$, 8 mM HEPES, and 10 mM glucose, pH 7.4) and incubated with 3 μM FLUO-4 in 0.1 mL loading buffer for 90 min. The cells are then washed twice with 0.2 mL loading buffer, resuspended in 0.1 mL of loading buffer, and transferred to a FLIPR for measurement of calcium mobilization flux in the presence of glutamate and in the presence or absence of a Piperidine Compound.

To measure calcium mobilization flux, fluoresence is monitored for about 15 s to establish a baseline and DMSO solutions containing various concentrations of a Piperidine Compound ranging from about 50 μM to about 0.8 nM diluted in loading buffer (0.05 mL of a 4X dilution) are added to the cell plate and fluoresence is monitored for about 2 min. 0.05 mL of a 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 μM and fluoresence is monitored for about 1 additional min. The final DMSO concentration in the assay is 1%. In each experiment fluoresence is monitored as a function of time and the data is analyzed using a non-linear regression to determine the IC_{50} value. In each experiment each data point is determined twice.

5.9 EXAMPLE 9: BINDING OF PIPERIDINE COMPOUNDS TO VR1

Methods for assaying compounds capable of inhibiting VR1 are known to those skilled in the art, for example, those methods disclosed in U.S. Patent No. 6,239,267 to Duckworth *et al.*; U.S. Patent No. 6,406,908 to McIntyre *et al.*; or U.S.

Patent No. 6,335,180 to Julius *et al.* The results of these assays will demonstrate that Piperidine Compounds bind to and modulate the activity of VR1.

Human VR1 Cloning: Human spinal cord RNA (commercially available from Clontech, Palo Alto, CA) is used. Reverse transcription is conducted on 1.0 μg total RNA using Thermoscript Reverse Transcriptase (commercially available from Invitrogen, Carlsbad, CA) and oligo dT primers as detailed in its product description. Reverse transcription reactions are incubated at 55°C for 1 h, heat-inactivated at 85°C for 5 min, and RNase H-treated at 37°C for 20 min.

Human VRl cDNA sequence is obtained by comparison of the human genomic sequence, prior to annotation, to the published rat sequence. Intron sequences are removed and flanking exonic sequences are joined to generate the hypothetical human cDNA. Primers flanking the coding region of human VR1 are designed as follows: forward primer, GAAGATCTTCGCTGGTTGCACACTGGGCCACA; and reverse primer, GAAGATCTTCGGGGACAGTGACGGTTGGATGT.

PCR of VRl is performed on one tenth of the Reverse transcription reaction mixture using Expand Long Template Polymerase and Expand Buffer 2 in a final volume of 50 μL according to the manufacturer's instructions (Roche Applied Sciences, Indianapolis, IN). After denaturation at 94°C for 2 min PCR amplification is performed for 25 cycles at 94°C for 15 sec, 58°C for 30 sec, and 68°C for 3 min followed by a final incubation at 72°C for 7 min to complete the amplification. A PCR product of ~2.8 kb is gel-isolated using a 1.0% agarose, Tris-Acetate gel containing 1.6 μg/mL of crystal violet and purified with a S.N.A.P. UV-Free Gel Purification Kit (commercially available from Invitrogen). The VR1 PCR product is cloned into the pIND/V5-His-TOPO vector (commercially available from Invitrogen) according to the manufacturer's instructions. DNA preparations, restriction enzyme digestions, and preliminary DNA sequencing are performed according to standard protocols. Full-length sequencing confirms the identity of the human VR1.

Generation of Inducible Cell Lines: Unless noted otherwise, cell culture reagents are purchased from Life Technologies of Rockville, MD. HEK293-EcR cells expressing the ecdysone receptor (commercially available from Invitrogen) are cultured in Growth Medium (Dulbecco's Modified Eagles Medium containing 10% fetal bovine serum (commercially available from HYCLONE, Logan, UT), lx penicillin/streptomycin, lx glutamine, 1 mM sodium pyruvate and 400 μg/mL Zeocin

(commercially available from Invitrogen)). The VR1-pIND constructs are transfected into the HEK293-EcR cell line using Fugene transfection reagent (commercially available from Roche Applied Sciences, Basel, Switzerland). After 48 h, cells are transferred to Selection Medium (Growth Medium containing 300 μg/mL G418 (commercially available from Invitrogen)). Approximately 3 weeks later individual Zeocin/G418 resistant colonies are isolated and expanded. To identify functional clones, multiple colonies are plated into 96-well plates and expression is induced for 48 h using Selection Medium supplemented with 5 μM ponasterone A ("PonA") (commercially available from Invitrogen). On the day of assay, cells are loaded with Fluo-4 (a calcium-sensitive dye that is commercially available from Molecular Probes, Eugene, OR) and CAP-mediated calcium influx is measured using a FLIPR as described below. Functional clones are re-assayed, expanded, and cryopreserved.

pH-Based Assay: Two days prior to performing this assay, cells are seeded on poly-D-lysine-coated 96-well clear-bottom black plates (commercially available from Becton-Dickinson) at 75,000 cells/well in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates are washed with 0.2 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 1.6 mM $CaCl_2$ and 20 mM HEPES, pH 7.4 ("wash buffer"), and loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final concentration, commercially available from Molecular Probes). After 1 h, the cells are washed twice with 0.2 mL wash buffer and resuspended in 0.05 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 3.5 mM $CaCl_2$ and 10 mM Citrate, pH 7.4 ("assay buffer"). Plates are then transferred to a FLIPR for assay. A Piperidine Compound is diluted in assay buffer, and 50 mL of the resultant solution are added to the cell plates and the solution is monitored for two minutes. The final concentration of the Piperidine Compound ranges from about 50 pM to about 3 μM. Agonist buffer (wash buffer titrated with 1N HCl to provide a solution having a pH of 5.5 when mixed 1:1 with assay buffer) (0.1 mL) is then added to each well, and the plates are incubated for 1 additional minute. Data are collected over the entire time course and analyzed using Excel and Graph Pad Prism.

Capsaicin-based Assay: Two days prior to performing this assay, cells are seeded in poly-D-lysine-coated 96-well clear-bottom black plates (50,000 cells/well) in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates are washed with 0.2 mL 1x

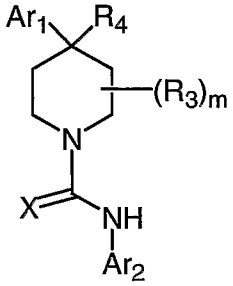
Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 1 mM $CaCl_2$ and 20 mM HEPES, pH 7.4, and cells are loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final). After one hour, the cells are washed twice with 0.2 mL of wash buffer and resuspended in 0.1 mL of wash buffer. The plates are transferred to a FLIPR for assay. 50 μL of the Piperidine Compound diluted with assay buffer are added to the cell plates and incubated for 2 min. The final concentration of the Piperidine Compound ranges from about 50 pM to about 3 μM. Human VR1 is activated by the addition of 50 μL of capsaicin (400 nM), and the plates are incubated for an additional 3 min. Data are collected over the entire time course and analyzed using Excel and GraphPad Prism.

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

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

What is claimed is:

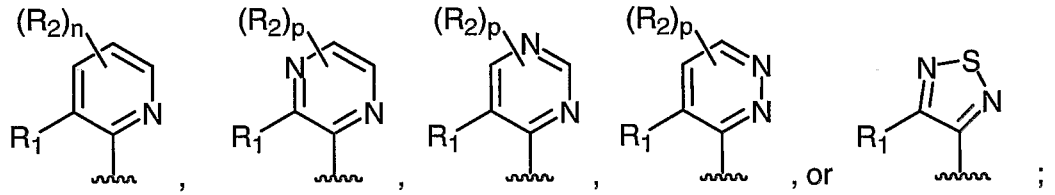
1. A compound of formula (I):



(I)

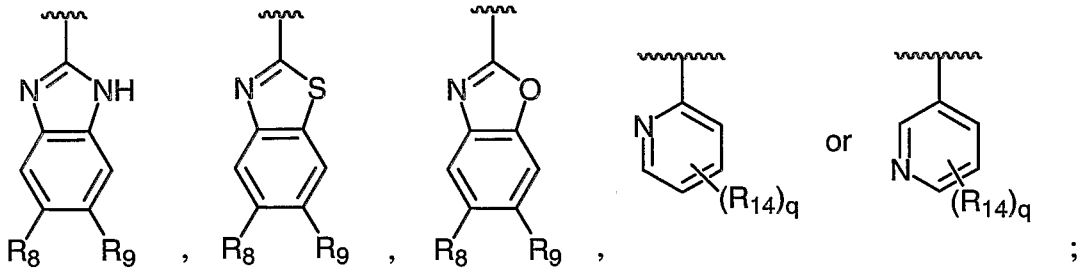
or a pharmaceutically acceptable salt thereof, wherein

Ar_1 is



;

Ar_2 is



;

X is O, S, N-CN, N-OH, or N-OR_{10};

R_1 is -H, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -OH, -CN, NO_2, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or

-(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, -NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

R_4 is -OH, -OCF_3, -halo, -(C_1-C_6)alkyl, -CH_2OH, -CH_2Cl, -CH_2Br, -CH_2I, -CH_2F, CH(halo)$_2$, -CF_3, -OR_{10}, -SR_{13}, -COOH, -$COOR_{10}$, -$C(O)R_{10}$, -C(O)H, -$OC(O)R_{10}$, -$OC(O)NHR_{10}$, -$NHC(O)R_{13}$, -$CON(R_{13})_2$, -SO_2R_{10}, or NO_2;

each R_5 is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -$CH{=}NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, or -$OC(O)OR_7$;

each R_6 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -$CH{=}NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

each R_7 is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or CH_2(halo);

each R_8 and R_9 are independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -CH_2C(halo)$_3$, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -$CH{=}NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

R_{10} is -(C_1-C_4)alkyl;

each R_{13} is independently:

(a) -H, or -(C_1-C_4)alkyl; or

(b) -phenyl or -(3- to 5-membered)heteroaryl each of which is unsubstituted or substituted with one or more R_6 groups;

each R_{14} is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-CH_2C(halo)_3$, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

each halo is independently -F, -Cl, -Br, or -I;

n is an integer ranging from 0 to 3;

p is an integer ranging from 0 to 2;

q is an integer ranging from 0 to 4; and

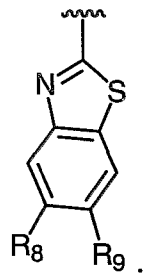
m is 0 or 1.

2. The compound of claim 1, wherein X is O and R_4 is -halo or -OH.

3. The compound of claim 2, wherein m is 0, n or p is 0, and Ar_1 is a pyridyl group or a pyridazinyl group.

4. The compound of claim 3, wherein R_1 is -Cl or $-CH_3$.

5. The compound of claim 4, wherein Ar_2 is



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6. The compound of claim 5, wherein R_8 and R_9 are -H.

7. The compound of claim 5, wherein R_8 is -H, and R_9 is a -(C_1-C_6)alkyl group or -halo.

8. The compound of claim 7, wherein the -(C_1-C_6)alkyl group is an *iso*-propyl group.

9. The compound of claim 7, wherein the -(C_1-C_6)alkyl group is a *tert*-butyl group.

10. The compound of claim 7, wherein R_9 is a -halo.

11. The compound of claim 10, wherein R_9 is a -F.

12. The compound of claim 10, wherein R_9 is a -Cl.

13. The compound of claim 10, wherein R_9 is a -Br.

14. The compound of claim 10, wherein R_9 is a -I.

15. The compound of claim 2, wherein Ar_1 is a pyridyl group.

16. The compound of claim 15, wherein R_1 is -Cl or $-CH_3$.

17. The compound of claim 16, wherein R_8 and R_9 are -H.

18. The compound of claim 16, wherein R_8 is -H, and R_9 is $-(C_1-C_6)$alkyl or -halo.

19. The compound of claim 18, wherein the $-(C_1-C_6)$alkyl group is an *iso*-propyl group.

20. The compound of claim 18, wherein the $-(C_1-C_6)$alkyl group is a *tert*-butyl group.

21. The compound of claim 18, wherein R_9 is a -halo.

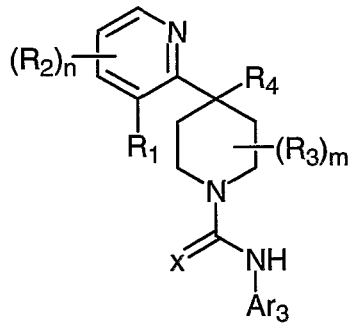
22. The compound of claim 18, wherein R_9 is -F.

23. The compound of claim 21, wherein R_9 is -Cl.

24. The compound of claim 21, wherein R_9 is -Br.

25. The compound of claim 21, wherein R_9 is -I.

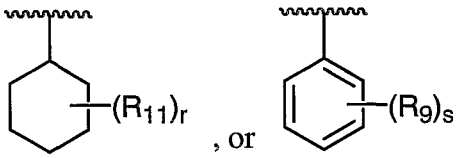
26. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

Ar_3 is



;

X is O, S, N-CN, N-OH, or N-OR_{10};

R_1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -OH, or $-NH_2$;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

R_4 is -OH, -OCF_3, -halo, -(C_1-C_6)alkyl, -CH_2OH, -CH_2Cl, -CH_2Br, -CH_2I, -CH_2F, $CH(halo)_2$, -CF_3, -OR_{10}, -SR_{13}, -COOH, -$COOR_{10}$, -$C(O)R_{10}$, -C(O)H, -$OC(O)R_{10}$, -$OC(O)NHR_{10}$, -$NHC(O)R_{13}$, -SO_2R_{10}, or NO_2;

each R_5 is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, or -$OC(O)OR_7$;

each R_6 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -$C(halo)_3$, -$CH(halo)_2$, -$CH_2(halo)$, -CN, -OH, -halo, -N_3, -NO_2, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

each R_7 is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -$C(halo)_3$, -$CH(halo)_2$, or $CH_2(halo)$;

each R_9 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -$CH_2C(halo)_3$, -$C(halo)_3$, -$CH(halo)_2$, -$CH_2(halo)$, -CN, -OH, -halo, -N_3, -NO_2, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

R_{10} is -(C_1-C_4)alkyl;

each R_{11} is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, or -$OC(O)OR_7$;

each R_{13} is independently:

(a) -H or -(C_1-C_4)alkyl; or

(b) -phenyl or -(3- to 5-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each halo is independently -F, -Cl, -Br, or -I;

n is an integer ranging from 0 to 3;

p is an integer ranging from 0 to 2;

r is an integer ranging from 0 to 6;

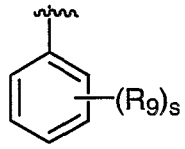
s is an integer ranging from 0 to 5; and

m is 0 or 1.

27. The compound of claim 26, wherein X is O and R_4 is -halo or -OH.

28. The compound of claim 27, wherein R_1 is $-CH_3$ or -halo.

29. The compound of claim 28, wherein Ar_3 is



30. The compound of claim 29, wherein s is 1 and R_9 is at the 4-position of the phenyl ring.

31. The compound of claim 29, wherein R_9 is a $-(C_1-C_6)$alkyl group or a -halo.

32. The compound of claim 31, wherein the $-(C_1-C_6)$alkyl group is an *iso*-propyl group.

33. The compound of claim 31, wherein the $-(C_1-C_6)$alkyl group is a *tert*-butyl group.

34. The compound of claim 31, wherein R_9 is a -halo.

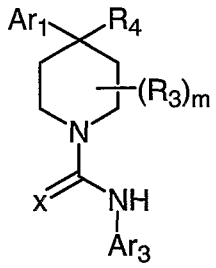
35. The compound of claim 34, wherein R_9 is -F.

36. The compound of claim 34, wherein R_9 is -Cl.

37. The compound of claim 34, wherein R_9 is -Br.

38. The compound of claim 34, wherein R_9 is -I.

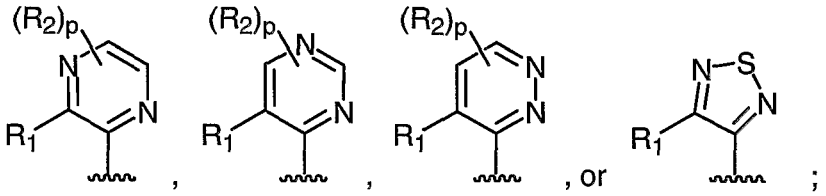
39. A compound of formula (III):



(III)

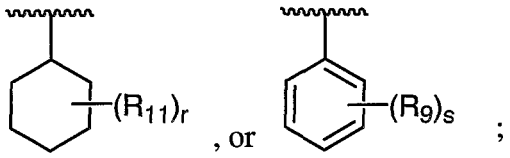
or a pharmaceutically acceptable salt thereof, wherein

Ar_1 is



;

Ar_3 is



;

X is O, S, N -CN, N-OH, or N-OR_{10};

R_1 is -H, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -OH, -CN, NO_2, or $-NH_2$;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

R_4 is -OH, -OCF_3, -halo, -(C_1-C_6)alkyl, -CH_2OH, -CH_2Cl, -CH_2Br, -CH_2I, -CH_2F, $CH(halo)_2$, -CF_3, -OR_{10}, -SR_{13}, -COOH, -$COOR_{10}$, -$C(O)R_{10}$, -C(O)H, -$OC(O)R_{10}$, -$OC(O)NHR_{10}$, -$NHC(O)R_{13}$, -SO_2R_{10}, or NO_2;

each R_5 is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, or -$OC(O)OR_7$;

each R_6 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -$C(halo)_3$, -$CH(halo)_2$, -$CH_2(halo)$, -CN, -OH, -halo, -N_3, -NO_2, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

each R_7 is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -$C(halo)_3$, -$CH(halo)_2$, or $CH_2(halo)$;

each R_9 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -$CH_2C(halo)_3$, -$C(halo)_3$, -$CH(halo)_2$, -$CH_2(halo)$, -CN, -OH, -halo, -N_3, -NO_2, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, -$OC(O)OR_7$, -SR_7, -$S(O)R_7$, or -$S(O)_2R_7$;

R_{10} is -(C_1-C_4)alkyl;

each R_{11} is independently -CN, -OH, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -$CH=NR_7$, -NR_7OH, -OR_7, -COR_7, -$C(O)OR_7$, -$OC(O)R_7$, or -$OC(O)OR_7$;

each R_{13} is independently:

(a) -H or -(C_1-C_4)alkyl; or

(b) -phenyl or -(3- to 5-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each halo is independently -F, -Cl, -Br, or -I;

p is an integer ranging from 0 to 2;

r is an integer ranging from 0-6;

s is an integer ranging from 0-5; and

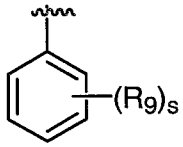
m is 0 or 1.

40. The compound of claim 39, wherein X is O and R_4 is -halo or -OH.

41. The compound of claim 40, wherein m is 0 p is 0, and Ar_1 is a pyridazinyl group.

42. The compound of claim 41, wherein R_1 is -Cl or $-CH_3$.

43. The compound of claim 42, wherein Ar_3 is



44. The compound of claim 44, wherein s is 1 and R_9 is at the 4-position of the phenyl ring.

45. The compound of claim 43, wherein R_9 is a -(C_1-C_6)alkyl group or a -halo.

46. The compound of claim 45, wherein the -(C_1-C_6)alkyl group is an *iso*-propyl group.

47. The compound of claim 46, wherein the -(C_1-C_6)alkyl group is a *tert*-butyl group.

48. The compound of claim 43, wherein R_9 is a -halo.

49. The compound of claim 45, wherein R_9 is -F.

50. The compound of claim 48, wherein R_9 is -Cl.

51. The compound of claim 48, wherein R_9 is -Br.

52. The compound of claim 48, wherein R_9 is -I.

53. A composition comprising the compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39 and a pharmaceutically acceptable carrier or excipient.

54. A method for treating or preventing pain in an animal, comprising administering to an animal in need thereof an effective amount of the compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39.

55. The method of claim 54, comprising administering to the animal an effective amount of another therapeutic agent.

56. A method for treating or preventing urinary incontinence in an animal, comprising administering to an animal in need thereof an effective amount of the compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39.

57. The method of claim 56, comprising administering to the animal an effective amount of another therapeutic agent.

58. A method for treating or preventing an ulcer in an animal, comprising administering to an animal in need thereof an effective amount of the compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39.

59. The method of claim 58, comprising administering to the animal an effective amount of another therapeutic agent.

60. A method for treating or preventing irritable-bowel syndrome in an animal, comprising administering to an animal in need thereof an effective amount of the compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39.

61. The method of claim 60, comprising administering to the animal an effective amount of another therapeutic agent.

62. A method for treating or preventing inflammatory-bowel disease in an animal, comprising administering to an animal in need thereof an effective amount of the

compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39.

63. The method of claim 62, comprising administering to the animal an effective amount of another therapeutic agent.

64. A method for inhibiting VR1 function in a cell comprising contacting a cell capable of expressing VR1 with an effective amount of the compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39.

65. A kit comprising a container containing an effective amount of the compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39.

66. A method for preparing a composition comprising the step of admixing a compound or a pharmaceutically acceptable salt of the compound of any of claims 1, 26, or 39 and a pharmaceutically acceptable carrier or excipient.