4-HETEROARYL-TETRAHYDROPIPERIDYL COMPOUNDS USEFUL FOR TREATING OR PREVENTING PAIN

This application claims the benefit of U.S. provisional application no. 60/489,516, filed July 24, 2003, the disclosure of the provisional application being incorporated by reference herein in its entirety.

1. FIELD OF THE INVENTION

The present invention relates to Tetrahydropiperidyl Compounds, compositions comprising an effective amount of a Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 cental nervous system and is maintained by aberrant somatosensory processing. There is a large body of evidence relating activity at both Group I mGluRs (mGluR1 and mGluR5) (M.E. Fundytus, *CNS Drugs* 15:29-58 (2001)) and vanilloid receptors (VR1) (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 *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).

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Urinary incontinence ("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, olsalazine, 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 lesions 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 97/28140 describes a class of piperidine compounds derived from 1-(piperazin-1-yl)aryl(oxy/amino)carbonyl-4-aryl-piperidine that are useful as 5-HT_{1Db} receptor antagonists.

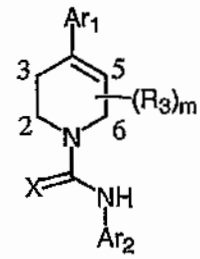
International publication no. WO 98/31677 describes a class of aromatic amines derived from cyclic amines that are useful as antidepressant drugs.

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.

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

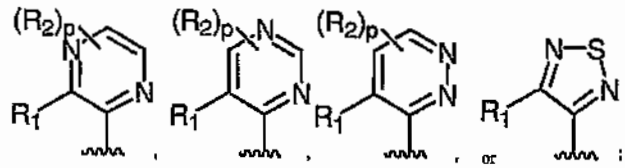
The present invention encompasses compounds of formula (I):



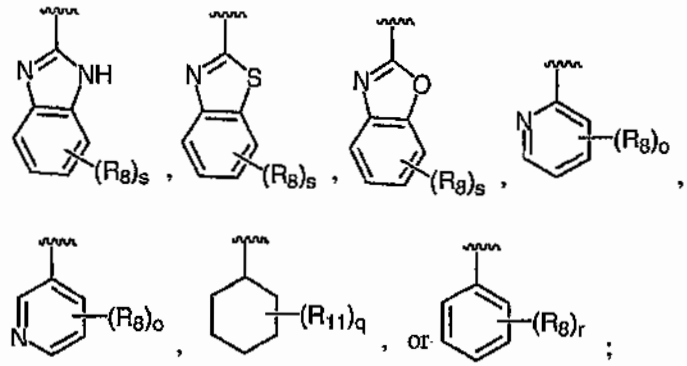
(I)

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, -NH_2, -CN, or -NO_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;

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, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$;

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, N$(R_7)_2$, -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 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, -$N(R_7)_2$, -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 -$(C_1$-$C_6)$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, -$N(R_7)_2$, -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;

m is 0 or 1;

o is an integer ranging 0 to 4;

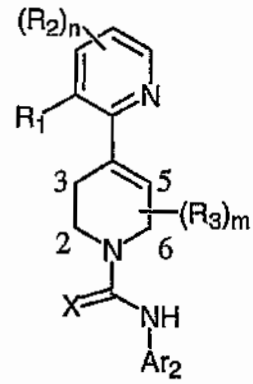
p is an integer ranging from 0 to 2;

q is an integer ranging from 0 to 6;

s is an integer ranging from 0 to 4; and

r is an integer ranging from 0 to 5.

The invention further encompasses compounds of formula (II)



(II)

and pharmaceutically acceptable salts thereof, where

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

X, R_2, R_3, Ar_2, and m are defined above for the compound of formula (I); and

n is an integer ranging from 0 to 3.

A compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof (a "Cycloheteroalkenyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl Compound.

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

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

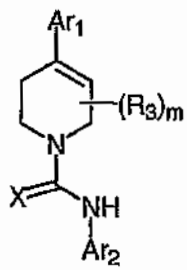
The invention still further relates to a kit comprising a container containing an effective amount of a Tetrahydropiperidyl Compound.

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 TETRAHYDROPIPERIDYL 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, X, and m are defined above for the Tetrahydropiperidyl Compounds of formula (I).

In one 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 thiadiazolyl 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.

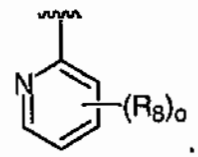
In another embodiment, X is N-OR_{10}.

In another embodiment, Ar_2 is a benzoimidazolyl group.

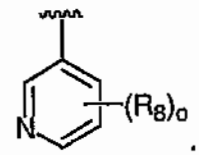
In another embodiment, Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_2 is a benzooxazolyl group.

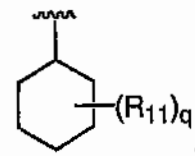
In another embodiment, Ar_2 is



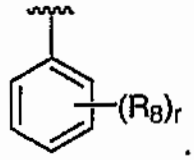
In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, p is 0.

In another embodiment, p is 1.

In another embodiment, o is 0.

In another embodiment, o is 1.

In another embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, r is 0.

In another embodiment, r 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, -OH, $-NH_2$, -CN, or $-NO_2$.

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.

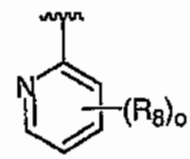
In another embodiment, Ar_2 is a benzothiazolyl group, benzoimidazolyl group, or benzooxazolyl group and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -C(O)R_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is a benzothiazolyl group and s is 1.

In another embodiment, Ar_2 is a benzoimidazolyl group and s is 1.

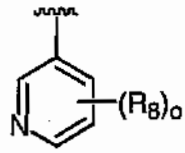
In another embodiment, Ar_2 is a benzooxazolyl group and s is 1.

In another embodiment, Ar_2 is



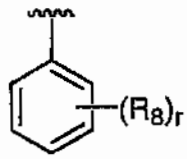
and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is



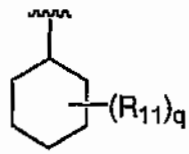
and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is



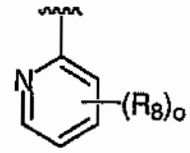
and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is



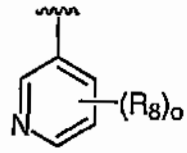
and each R_{11} is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is



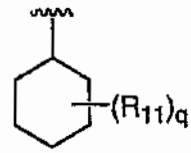
and o is 1.

In another embodiment, Ar_2 is



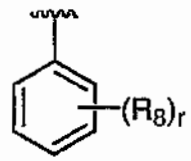
and o is 1.

In another embodiment, Ar_2 is



and q is 1.

In another embodiment, Ar_2 is



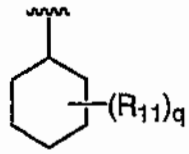
and r is 1.

In another embodiment, Ar_1 is a pyrazinyl group, X is O, m is 0, and Ar_2 is a benzothiazolyl group.

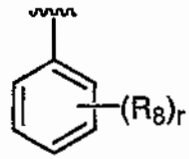
In another embodiment, Ar_1 is a pyrazinyl group, X is O, m is 0, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyrazinyl group, X is O, m is 0, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyrazinyl group, X is O, m is 0, and Ar_2 is



In another embodiment, Ar_1 is a pyrazinyl group, X is O, m is 0, and Ar_2 is

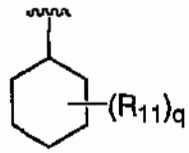


In another embodiment, Ar_1 is a pyrimidinyl group, X is O, m is 0, and Ar_2 is a benzothiazolyl group.

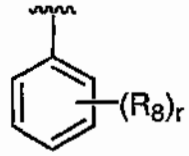
In another embodiment, Ar_1 is a pyrimidinyl group, X is O, m is 0, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a pyrimidinyl group, X is O, m is 0, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a pyrimidinyl group, X is O, m is 0, and Ar_2 is



In another embodiment, Ar_1 is a pyrimidinyl group, X is O, m is 0, and Ar_2 is

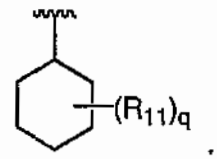


In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, and Ar_2 is a benzothiazolyl group.

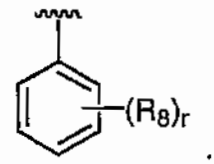
In another embodiment, Ar_1 is a pyridazinyl group, X is O, m is 0, and Ar_2 is a benzooxazolyl group.

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

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



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

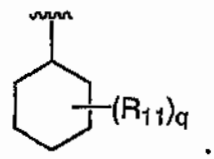


In another embodiment, Ar_1 is a thiadiazolyl group, X is O, m is 0, and Ar_2 is a benzothiazolyl group.

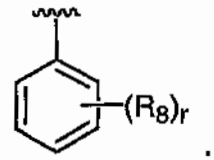
In another embodiment, Ar_1 is a thiadiazolyl group, X is O, m is 0, and Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_1 is a thiadiazolyl group, X is O, m is 0, and Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_1 is a thiadiazolyl group, X is O, m is 0, and Ar_2 is

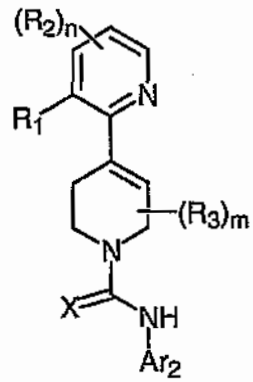


In another embodiment, Ar_1 is a thiadiazolyl group, X is O, m is 0, and Ar_2 is



4.2 TETRAHYDROPIPERIDYL COMPOUNDS OF FORMULA (II)

The invention also relates to Tetrahydropiperidyl Compounds of formula (II)



(II)

and pharmaceutically acceptable salts thereof, where R_1, R_2, R_3, Ar_2, X, n and m are defined above for the Tetrahydropiperidyl 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.

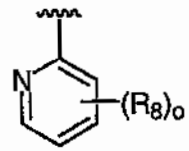
In another embodiment, X is N-OR_{10}.

In another embodiment, Ar_2 is a benzoimidazolyl group.

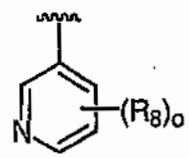
In another embodiment, Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_2 is a benzooxazolyl group.

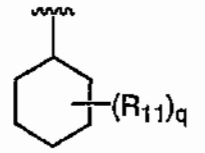
In another embodiment, Ar_2 is



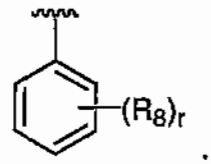
In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, n is 3.

In another embodiment, o is 0.

In another embodiment, o is 1.

In another embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, r is 0.

In another embodiment, r 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, -NH$_2$, -CN, or -NO$_2$.

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)heterocycle, 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$_3$.

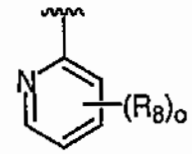
In another embodiment, Ar_2 is a benzothiazolyl group, benzoimidazolyl group, or benzooxazolyl group and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH$_2$(halo), -CN, -OH, -halo, -N$_3$, -NO$_2$, -N(R_7)$_2$, -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)$_2$$R_7$.

In another embodiment, Ar_2 is a benzothiazolyl group and s is 1.

In another embodiment, Ar_2 is a benzoimidazolyl group and s is 1.

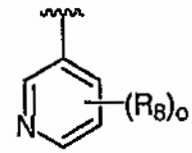
In another embodiment, Ar_2 is a benzooxazolyl group and s is 1.

In another embodiment, Ar_2 is



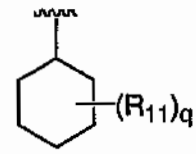
and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is



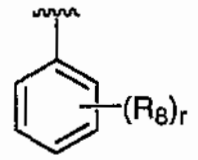
and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is



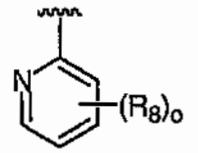
and each R_{11} is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$.

In another embodiment, Ar_2 is



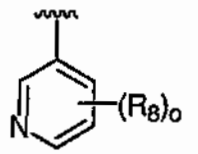
and each R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -C(O)R_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$.

In another embodiment, Ar_2 is



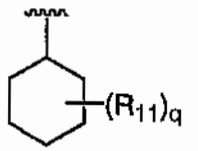
and o is 1.

In another embodiment, Ar_2 is



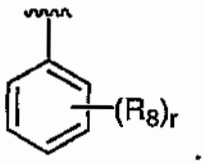
and o is 1.

In another embodiment, Ar_2 is



and q is 1.

In another embodiment, Ar_2 is



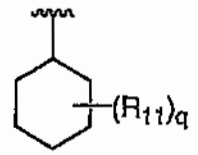
and r is 1.

In another embodiment, X is O, m is 0, and Ar_2 is a benzothiazolyl group.

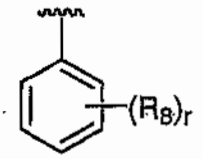
In another embodiment, X is O, m is 0, and Ar_2 is a benzooxazolyl group.

In another embodiment, X is O, m is 0, and Ar_2 is a benzoimidazolyl group.

In another embodiment, X is O, m is 0, and Ar_2 is



In another embodiment, X is O, m is 0, and Ar_2 is



In the Tetrahydropiperidyl Compounds that have an R_3 group, the R_3 group can be attached to the carbon atom at the 2-, 3-, 5- or 6-position of the Tetrahydropiperidyl ring. In one embodiment, the R_3 group is attached to the carbon at the 2-position of the Tetrahydropiperidyl ring. In another embodiment, the R_3 group is attached to the carbon at the 3-position of the Tetrahydropiperidyl ring. In another embodiment, the R_3 group is attached to the carbon at the 6-position of the Tetrahydropiperidyl ring. In another embodiment, the R_3 group is attached to the carbon at the 5-position of the Tetrahydropiperidyl ring.

In one embodiment, the Tetrahydropiperidyl Compound has an R_3 group; the carbon atom to which the R_3 group is attached is at the 2-, 3- or 6-position of the Tetrahydropiperidyl ring; and the carbon atom to which the R_3 group is attached has the (R) configuration. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group; the carbon atom to which the R_3 group is attached is at the 2-, 3- or 6-position of the Tetrahydropiperidyl ring; and the carbon atom to which the R_3 group is attached has the (S) configuration.

In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring. The R_3 group is in the (R) configuration, and R_3 is -CH_2CH_3.

In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon that is at the 2-position of the Tetrahydropiperidyl ring, the carbon to which the R_3 group is attached is in the (S) configuration, and R_3 is -CH_2CH_3.

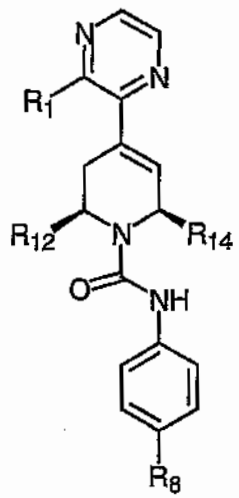
In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 3-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, 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 Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 6-position of the Tetrahydropiperidyl ring, the carbon atom to which the R_3 grooup is attached is in the (S) configuration, and R_3 is $-CH_2CH_3$.

In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 5-position of the Tetrahydropiperidyl ring and R_3 is -(C_1-C_4) alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 5-position of the Tetrahydropiperidyl ring and R_3 is $-CH_3$. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 5-position of the Tetrahydropiperidyl ring and R_3 is $-CF_3$. In another embodiment, the Tetrahydropiperidyl Compound has an R_3 group, the R_3 group is attached to the carbon atom at the 5-position of the Tetrahydropiperidyl ring and R_3 is $-CH_2CH_3$.

Illustrative Tetrahydropiperidyl Compounds are listed below in Tables 1-10:

Table 1



(Ia)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8
A01(a), (b), and (c)	-H	-H
A02(a), (b), and (c)	-H	-*tert*-butyl
A03(a), (b), and (c)	-H	-*iso*-butyl
A04(a), (b), and (c)	-H	-*sec*-butyl
A05(a), (b), and (c)	-H	-*iso*-propyl
A06(a), (b), and (c)	-H	-n-propyl
A07(a), (b), and (c)	-H	-cyclohexyl
A08(a), (b), and (c)	-H	-*tert*-butoxy
A09(a), (b), and (c)	-H	-*iso*-propoxy
A10(a), (b), and (c)	-H	$-CF_3$
A11(a), (b), and (c)	-H	$-CH_2CF_3$
A12(a), (b), and (c)	-H	$-OCF_3$
A13(a), (b), and (c)	-H	-Cl
A14(a), (b), and (c)	-H	-Br
A15(a), (b), and (c)	-H	-I
A16(a), (b), and (c)	-H	-n-butyl
A17(a), (b), and (c)	-H	-n-propyl
A18(a), (b), and (c)	-Cl	-H
A19(a), (b), and (c)	-Cl	-*tert*-butyl
A20(a), (b), and (c)	-Cl	-*iso*-butyl
A21(a), (b), and (c)	-Cl	-*sec*-butyl
A22(a), (b), and (c)	-Cl	-*iso*-propyl
A23(a), (b), and (c)	-Cl	-n-propyl
A24(a), (b), and (c)	-Cl	-cyclohexyl
A25(a), (b), and (c)	-Cl	-*tert*-butoxy

A26(a), (b), and (c)	-Cl	-*iso*-propoxy
A27(a), (b), and (c)	-Cl	$-CF_3$
A28(a), (b), and (c)	-Cl	$-CH_2CF_3$
A29(a), (b), and (c)	-Cl	$-OCF_3$
A30(a), (b), and (c)	-Cl	-Cl
A31(a), (b), and (c)	-Cl	-Br
A32(a), (b), and (c)	-Cl	-I
A33(a), (b), and (c)	-Cl	-n-butyl
A34(a), (b), and (c)	-Cl	-n-propyl
A35(a), (b), and (c)	-F	-H
A36(a), (b), and (c)	-F	-*tert*-butyl
A37(a), (b), and (c)	-F	-*iso*-butyl
A38(a), (b), and (c)	-F	-*sec*-butyl
A39(a), (b), and (c)	-F	-*iso*-propyl
A40(a), (b), and (c)	-F	-n-propyl
A41(a), (b), and (c)	-F	-cyclohexyl
A42(a), (b), and (c)	-F	-*tert*-butoxy
A43(a), (b), and (c)	-F	-*iso*-propoxy
A44(a), (b), and (c)	-F	$-CF_3$
A45(a), (b), and (c)	-F	$-CH_2CF_3$
A46(a), (b), and (c)	-F	$-OCF_3$
A47(a), (b), and (c)	-F	-Cl
A48(a), (b), and (c)	-F	-Br
A49(a), (b), and (c)	-F	-I
A50(a), (b), and (c)	-F	-n-butyl
A51(a), (b), and (c)	-F	-n-propyl
A52(a), (b), and (c)	$-CH_3$	-H
A53(a), (b), and (c)	$-CH_3$	-*iso*-butyl
A54(a), (b), and (c)	$-CH_3$	-*tert*-butyl
A55(a), (b), and (c)	$-CH_3$	-*sec*-butyl
A56(a), (b), and (c)	$-CH_3$	-*iso*-propyl
A57(a), (b), and (c)	$-CH_3$	-n-propyl
A58(a), (b), and (c)	$-CH_3$	-cyclohexyl
A59(a), (b), and (c)	$-CH_3$	-*tert*-butoxy
A60(a), (b), and (c)	$-CH_3$	-*iso*-propoxy
A61(a), (b), and (c)	$-CH_3$	$-CF_3$
A62(a), (b), and (c)	$-CH_3$	$-CH_2CF_3$
A63(a), (b), and (c)	$-CH_3$	$-OCF_3$
A64(a), (b), and (c)	$-CH_3$	-Cl
A65(a), (b), and (c)	$-CH_3$	-Br
A66(a), (b), and (c)	$-CH_3$	-I
A67(a), (b), and (c)	$-CH_3$	-n-butyl
A68(a), (b), and (c)	$-CH_3$	-n-propyl
A69(a), (b), and (c)	$-CF_3$	-H
A70(a), (b), and (c)	$-CF_3$	-*tert*-butyl
A71(a), (b), and (c)	$-CF_3$	-*iso*-butyl
A72(a), (b), and (c)	$-CF_3$	-*sec*-butyl
A73(a), (b), and (c)	$-CF_3$	-*iso*-propyl

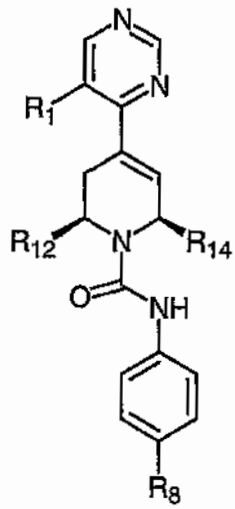
A74(a), (b), and (c)	$-CF_3$	-n-propyl
A75(a), (b), and (c)	$-CF_3$	-cyclohexyl
A76(a), (b), and (c)	$-CF_3$	-*tert*-butoxy
A77(a), (b), and (c)	$-CF_3$	-*iso*-propoxy
A78(a), (b), and (c)	$-CF_3$	$-CF_3$
A79(a), (b), and (c)	$-CF_3$	$-CH_2CF_3$
A80(a), (b), and (c)	$-CF_3$	$-OCF_3$
A81(a), (b), and (c)	$-CF_3$	-Cl
A82(a), (b), and (c)	$-CF_3$	-Br
A83(a), (b), and (c)	$-CF_3$	-I
A84(a), (b), and (c)	$-CF_3$	-n-butyl
A85(a), (b), and (c)	$-CF_3$	-n-propyl
A86(a), (b), and (c)	$-CHF_2$	-*tert*-butyl
A87(a), (b), and (c)	$-CHF_2$	-H
A88(a), (b), and (c)	$-CHF_2$	-*iso*-butyl
A89(a), (b), and (c)	$-CHF_2$	-*sec*-butyl
A90(a), (b), and (c)	$-CHF_2$	-*iso*-propyl
A91(a), (b), and (c)	$-CHF_2$	-n-propyl
A92(a), (b), and (c)	$-CHF_2$	-cyclohexyl
A93(a), (b), and (c)	$-CHF_2$	-*tert*-butoxy
A94(a), (b), and (c)	$-CHF_2$	-*iso*-propoxy
A95(a), (b), and (c)	$-CHF_2$	$-CF_3$
A96(a), (b), and (c)	$-CHF_2$	$-CH_2CF_3$
A97(a), (b), and (c)	$-CHF_2$	$-OCF_3$
A98(a), (b), and (c)	$-CHF_2$	-Cl
A99(a), (b), and (c)	$-CHF_2$	-Br
A100(a), (b), and (c)	$-CHF_2$	-I
A101(a), (b), and (c)	$-CHF_2$	-n-butyl
A102(a), (b), and (c)	$-CHF_2$	-n-propyl
A103(a), (b), and (c)	-OH	-H
A104(a), (b), and (c)	-OH	-*tert*-butyl
A105(a), (b), and (c)	-OH	-*iso*-butyl
A106(a), (b), and (c)	-OH	-*sec*-butyl
A107(a), (b), and (c)	-OH	-*iso*-propyl
A108(a), (b), and (c)	-OH	-n-propyl
A109(a), (b), and (c)	-OH	-cyclohexyl
A110(a), (b), and (c)	-OH	-*tert*-butoxy
A111(a), (b), and (c)	-OH	-*iso*-propoxy
A112(a), (b), and (c)	-OH	$-CF_3$
A113(a), (b), and (c)	-OH	$-CH_2CF_3$
A114(a), (b), and (c)	-OH	$-OCF_3$
A115(a), (b), and (c)	-OH	-Cl
A116(a), (b), and (c)	-OH	-Br
A117(a), (b), and (c)	-OH	-I
A118(a), (b), and (c)	-OH	-n-butyl
A119(a), (b), and (c)	-OH	-n-propyl
A120(a), (b), and (c)	$-NO_2$	-H
A121(a), (b), and (c)	$-NO_2$	-*tert*-butyl

A122(a), (b), and (c)	$-NO_2$	-*iso*-butyl
A123(a), (b), and (c)	$-NO_2$	-*sec*-butyl
A124(a), (b), and (c)	$-NO_2$	-*iso*-propyl
A125(a), (b), and (c)	$-NO_2$	-n-propyl
A126(a), (b), and (c)	$-NO_2$	-cyclohexyl
A127(a), (b), and (c)	$-NO_2$	-*tert*-butoxy
A128(a), (b), and (c)	$-NO_2$	-*iso*-propoxy
A129(a), (b), and (c)	$-NO_2$	$-CF_3$
A130(a), (b), and (c)	$-NO_2$	$-CH_2CF_3$
A131(a), (b), and (c)	$-NO_2$	$-OCF_3$
A132(a), (b), and (c)	$-NO_2$	-Cl
A133(a), (b), and (c)	$-NO_2$	-Br
A134(a), (b), and (c)	$-NO_2$	-I
A135(a), (b), and (c)	$-NO_2$	-n-butyl
A136(a), (b), and (c)	$-NO_2$	-n-propyl
A137(a), (b), and (c)	-CN	-H
A138(a), (b), and (c)	-CN	-*tert*-butyl
A139(a), (b), and (c)	-CN	-*iso*-butyl
A140(a), (b), and (c)	-CN	-*sec*-butyl
A141(a), (b), and (c)	-CN	-*iso*-propyl
A142(a), (b), and (c)	-CN	-n-propyl
A143(a), (b), and (c)	-CN	-cyclohexyl
A144(a), (b), and (c)	-CN	-*tert*-butoxy
A145(a), (b), and (c)	-CN	-*iso*-propoxy
A146(a), (b), and (c)	-CN	$-CF_3$
A147(a), (b), and (c)	-CN	$-CH_2CF_3$
A148(a), (b), and (c)	-CN	$-OCF_3$
A149(a), (b), and (c)	-CN	-Cl
A150(a), (b), and (c)	-CN	-Br
A151(a), (b), and (c)	-CN	-I
A152(a), (b), and (c)	-CN	-n-butyl
A153(a), (b), and (c)	-CN	-n-propyl
A154(a), (b), and (c)	-Br	-H
A155(a), (b), and (c)	-Br	-*tert*-butyl
A156(a), (b), and (c)	-Br	-*iso*-butyl
A157(a), (b), and (c)	-Br	-*sec*-butyl
A158(a), (b), and (c)	-Br	-*iso*-propyl
A159(a), (b), and (c)	-Br	-n-propyl
A160(a), (b), and (c)	-Br	-cyclohexyl
A161(a), (b), and (c)	-Br	-*tert*-butoxy
A162(a), (b), and (c)	-Br	-*iso*-propoxy
A163(a), (b), and (c)	-Br	$-CF_3$
A164(a), (b), and (c)	-Br	$-CH_2CF_3$
A165(a), (b), and (c)	-Br	$-OCF_3$
A166(a), (b), and (c)	-Br	-Cl
A167(a), (b), and (c)	-Br	-Br
A168(a), (b), and (c)	-Br	-I
A169(a), (b), and (c)	-Br	-n-butyl

A170(a), (b), and (c)	-Br	-n-propyl
A171(a), (b), and (c)	-I	-*tert*-butyl
A172(a), (b), and (c)	-I	-H
A173(a), (b), and (c)	-I	-*iso*-butyl
A174(a), (b), and (c)	-I	-*sec*-butyl
A175(a), (b), and (c)	-I	-*iso*-propyl
A176(a), (b), and (c)	-I	-n-propyl
A177(a), (b), and (c)	-I	-cyclohexyl
A178(a), (b), and (c)	-I	-*tert*-butoxy
A179(a), (b), and (c)	-I	-*iso*-propoxy
A180(a), (b), and (c)	-I	$-CF_3$
A181(a), (b), and (c)	-I	$-CH_2CF_3$
A182(a), (b), and (c)	-I	$-OCF_3$
A183(a), (b), and (c)	-I	-Cl
A184(a), (b), and (c)	-I	-Br
A185(a), (b), and (c)	-I	-I
A186(a), (b), and (c)	-I	-n-butyl
A187(a), (b), and (c)	-I	-n-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 2



(Ib)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8
B01(a), (b), and (c)	-H	-H
B02(a), (b), and (c)	-H	-*tert*-butyl
B03(a), (b), and (c)	-H	-*iso*-butyl
B04(a), (b), and (c)	-H	-*sec*-butyl
B05(a), (b), and (c)	-H	-*iso*-propyl
B06(a), (b), and (c)	-H	-n-propyl
B07(a), (b), and (c)	-H	-cyclohexyl
B08(a), (b), and (c)	-H	-*tert*-butoxy
B09(a), (b), and (c)	-H	-*iso*-propoxy
B10(a), (b), and (c)	-H	$-CF_3$
B11(a), (b), and (c)	-H	$-CH_2CF_3$
B12(a), (b), and (c)	-H	$-OCF_3$
B13(a), (b), and (c)	-H	-Cl
B14(a), (b), and (c)	-H	-Br
B15(a), (b), and (c)	-H	-I
B16(a), (b), and (c)	-H	-n-butyl
B17(a), (b), and (c)	-H	-n-propyl
B18(a), (b), and (c)	-Cl	-H
B19(a), (b), and (c)	-Cl	-*tert*-butyl
B20(a), (b), and (c)	-Cl	-*iso*-butyl
B21(a), (b), and (c)	-Cl	-*sec*-butyl
B22(a), (b), and (c)	-Cl	-*iso*-propyl
B23(a), (b), and (c)	-Cl	-n-propyl
B24(a), (b), and (c)	-Cl	-cyclohexyl

B25(a), (b), and (c)	-Cl	-*tert*-butoxy
B26(a), (b), and (c)	-Cl	-*iso*-propoxy
B27(a), (b), and (c)	-Cl	$-CF_3$
B28(a), (b), and (c)	-Cl	$-CH_2CF_3$
B29(a), (b), and (c)	-Cl	$-OCF_3$
B30(a), (b), and (c)	-Cl	-Cl
B31(a), (b), and (c)	-Cl	-Br
B32(a), (b), and (c)	-Cl	-I
B33(a), (b), and (c)	-Cl	-n-butyl
B34(a), (b), and (c)	-Cl	-n-propyl
B35(a), (b), and (c)	-F	-H
B36(a), (b), and (c)	-F	-*tert*-butyl
B37(a), (b), and (c)	-F	-*iso*-butyl
B38(a), (b), and (c)	-F	-*sec*-butyl
B39(a), (b), and (c)	-F	-*iso*-propyl
B40(a), (b), and (c)	-F	-n-propyl
B41(a), (b), and (c)	-F	-cyclohexyl
B42(a), (b), and (c)	-F	-*tert*-butoxy
B43(a), (b), and (c)	-F	-*iso*-propoxy
B44(a), (b), and (c)	-F	$-CF_3$
B45(a), (b), and (c)	-F	$-CH_2CF_3$
B46(a), (b), and (c)	-F	$-OCF_3$
B47(a), (b), and (c)	-F	-Cl
B48(a), (b), and (c)	-F	-Br
B49(a), (b), and (c)	-F	-I
B50(a), (b), and (c)	-F	-n-butyl
B51(a), (b), and (c)	-F	-n-propyl
B52(a), (b), and (c)	$-CH_3$	-H
B53(a), (b), and (c)	$-CH_3$	-*iso*-butyl
B54(a), (b), and (c)	$-CH_3$	-*tert*-butyl
B55(a), (b), and (c)	$-CH_3$	-*sec*-butyl
B56(a), (b), and (c)	$-CH_3$	-*iso*-propyl
B57(a), (b), and (c)	$-CH_3$	-n-propyl
B58(a), (b), and (c)	$-CH_3$	-cyclohexyl
B59(a), (b), and (c)	$-CH_3$	-*tert*-butoxy
B60(a), (b), and (c)	$-CH_3$	-*iso*-propoxy
B61(a), (b), and (c)	$-CH_3$	$-CF_3$
B62(a), (b), and (c)	$-CH_3$	$-CH_2CF_3$
B63(a), (b), and (c)	$-CH_3$	$-OCF_3$
B64(a), (b), and (c)	$-CH_3$	-Cl
B65(a), (b), and (c)	$-CH_3$	-Br
B66(a), (b), and (c)	$-CH_3$	-I
B67(a), (b), and (c)	$-CH_3$	-n-butyl
B68(a), (b), and (c)	$-CH_3$	-n-propyl
B69(a), (b), and (c)	$-CF_3$	-H
B70(a), (b), and (c)	$-CF_3$	-*tert*-butyl
B71(a), (b), and (c)	$-CF_3$	-*iso*-butyl
B72(a), (b), and (c)	$-CF_3$	-*sec*-butyl

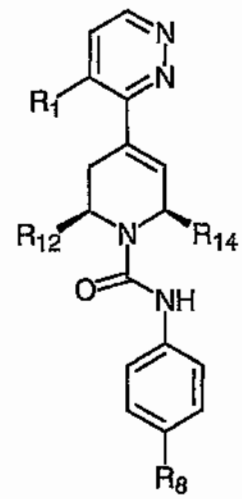
B73(a), (b), and (c)	$-CF_3$	-*iso*-propyl
B74(a), (b), and (c)	$-CF_3$	-n-propyl
B75(a), (b), and (c)	$-CF_3$	-cyclohexyl
B76(a), (b), and (c)	$-CF_3$	-*tert*-butoxy
B77(a), (b), and (c)	$-CF_3$	-*iso*-propoxy
B78(a), (b), and (c)	$-CF_3$	$-CF_3$
B79(a), (b), and (c)	$-CF_3$	$-CH_2CF_3$
B80(a), (b), and (c)	$-CF_3$	$-OCF_3$
B81(a), (b), and (c)	$-CF_3$	-Cl
B82(a), (b), and (c)	$-CF_3$	-Br
B83(a), (b), and (c)	$-CF_3$	-I
B84(a), (b), and (c)	$-CF_3$	-n-butyl
B85(a), (b), and (c)	$-CF_3$	-n-propyl
B86(a), (b), and (c)	$-CHF_2$	-*tert*-butyl
B87(a), (b), and (c)	$-CHF_2$	-H
B88(a), (b), and (c)	$-CHF_2$	-*iso*-butyl
B89(a), (b), and (c)	$-CHF_2$	-*sec*-butyl
B90(a), (b), and (c)	$-CHF_2$	-*iso*-propyl
B91(a), (b), and (c)	$-CHF_2$	-n-propyl
B92(a), (b), and (c)	$-CHF_2$	-cyclohexyl
B93(a), (b), and (c)	$-CHF_2$	-*tert*-butoxy
B94(a), (b), and (c)	$-CHF_2$	-*iso*-propoxy
B95(a), (b), and (c)	$-CHF_2$	$-CF_3$
B96(a), (b), and (c)	$-CHF_2$	$-CH_2CF_3$
B97(a), (b), and (c)	$-CHF_2$	$-OCF_3$
B98(a), (b), and (c)	$-CHF_2$	-Cl
B99(a), (b), and (c)	$-CHF_2$	-Br
B100(a), (b), and (c)	$-CHF_2$	-I
B101(a), (b), and (c)	$-CHF_2$	-n-butyl
B102(a), (b), and (c)	$-CHF_2$	-n-propyl
B103(a), (b), and (c)	-OH	-H
B104(a), (b), and (c)	-OH	-*tert*-butyl
B105(a), (b), and (c)	-OH	-*iso*-butyl
B106(a), (b), and (c)	-OH	-*sec*-butyl
B107(a), (b), and (c)	-OH	-*iso*-propyl
B108(a), (b), and (c)	-OH	-n-propyl
B109(a), (b), and (c)	-OH	-cyclohexyl
B110(a), (b), and (c)	-OH	-*tert*-butoxy
B111(a), (b), and (c)	-OH	-*iso*-propoxy
B112(a), (b), and (c)	-OH	$-CF_3$
B113(a), (b), and (c)	-OH	$-CH_2CF_3$
B114(a), (b), and (c)	-OH	$-OCF_3$
B115(a), (b), and (c)	-OH	-Cl
B116(a), (b), and (c)	-OH	-Br
B117(a), (b), and (c)	-OH	-I
B118(a), (b), and (c)	-OH	-n-butyl
B119(a), (b), and (c)	-OH	-n-propyl
B120(a), (b), and (c)	$-NO_2$	-H

B121(a), (b), and (c)	$-NO_2$	-*tert*-butyl
B122(a), (b), and (c)	$-NO_2$	-*iso*-butyl
B123(a), (b), and (c)	$-NO_2$	-*sec*-butyl
B124(a), (b), and (c)	$-NO_2$	-*iso*-propyl
B125(a), (b), and (c)	$-NO_2$	-n-propyl
B126(a), (b), and (c)	$-NO_2$	-cyclohexyl
B127(a), (b), and (c)	$-NO_2$	-*tert*-butoxy
B128(a), (b), and (c)	$-NO_2$	-*iso*-propoxy
B129(a), (b), and (c)	$-NO_2$	$-CF_3$
B130(a), (b), and (c)	$-NO_2$	$-CH_2CF_3$
B131(a), (b), and (c)	$-NO_2$	$-OCF_3$
B132(a), (b), and (c)	$-NO_2$	-Cl
B133(a), (b), and (c)	$-NO_2$	-Br
B134(a), (b), and (c)	$-NO_2$	-I
B135(a), (b), and (c)	$-NO_2$	-n-butyl
B136(a), (b), and (c)	$-NO_2$	-n-propyl
B137(a), (b), and (c)	-CN	-H
B138(a), (b), and (c)	-CN	-*tert*-butyl
B139(a), (b), and (c)	-CN	-*iso*-butyl
B140(a), (b), and (c)	-CN	-*sec*-butyl
B141(a), (b), and (c)	-CN	-*iso*-propyl
B142(a), (b), and (c)	-CN	-n-propyl
B143(a), (b), and (c)	-CN	-cyclohexyl
B144(a), (b), and (c)	-CN	-*tert*-butoxy
B145(a), (b), and (c)	-CN	-*iso*-propoxy
B146(a), (b), and (c)	-CN	$-CF_3$
B147(a), (b), and (c)	-CN	$-CH_2CF_3$
B148(a), (b), and (c)	-CN	$-OCF_3$
B149(a), (b), and (c)	-CN	-Cl
B150(a), (b), and (c)	-CN	-Br
B151(a), (b), and (c)	-CN	-I
B152(a), (b), and (c)	-CN	-n-butyl
B153(a), (b), and (c)	-CN	-n-propyl
B154(a), (b), and (c)	-Br	-H
B155(a), (b), and (c)	-Br	-*tert*-butyl
B156(a), (b), and (c)	-Br	-*iso*-butyl
B157(a), (b), and (c)	-Br	-*sec*-butyl
B158(a), (b), and (c)	-Br	-*iso*-propyl
B159(a), (b), and (c)	-Br	-n-propyl
B160(a), (b), and (c)	-Br	-cyclohexyl
B161(a), (b), and (c)	-Br	-*tert*-butoxy
B162(a), (b), and (c)	-Br	-*iso*-propoxy
B163(a), (b), and (c)	-Br	$-CF_3$
B164(a), (b), and (c)	-Br	$-CH_2CF_3$
B165(a), (b), and (c)	-Br	$-OCF_3$
B166(a), (b), and (c)	-Br	-Cl
B167(a), (b), and (c)	-Br	-Br
B168(a), (b), and (c)	-Br	-I

B169(a), (b), and (c)	-Br	-n-butyl
B170(a), (b), and (c)	-Br	-n-propyl
B171(a), (b), and (c)	-I	-*tert*-butyl
B172(a), (b), and (c)	-I	-H
B173(a), (b), and (c)	-I	-*iso*-butyl
B174(a), (b), and (c)	-I	-*sec*-butyl
B175(a), (b), and (c)	-I	-*iso*-propyl
B176(a), (b), and (c)	-I	-n-propyl
B177(a), (b), and (c)	-I	-cyclohexyl
B178(a), (b), and (c)	-I	-*tert*-butoxy
B179(a), (b), and (c)	-I	-*iso*-propoxy
B180(a), (b), and (c)	-I	$-CF_3$
B181(a), (b), and (c)	-I	$-CH_2CF_3$
B182(a), (b), and (c)	-I	$-OCF_3$
B183(a), (b), and (c)	-I	-Cl
B184(a), (b), and (c)	-I	-Br
B185(a), (b), and (c)	-I	-I
B186(a), (b), and (c)	-I	-n-butyl
B187(a), (b), and (c)	-I	-n-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 3



(Ic)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8
C01(a), (b), and (c)	-H	-H
C02(a), (b), and (c)	-H	-*tert*-butyl
C03(a), (b), and (c)	-H	-*iso*-butyl
C04(a), (b), and (c)	-H	-*sec*-butyl
C05(a), (b), and (c)	-H	-*iso*-propyl
C06(a), (b), and (c)	-H	-n-propyl
C07(a), (b), and (c)	-H	-cyclohexyl
C08(a), (b), and (c)	-H	-*tert*-butoxy
C09(a), (b), and (c)	-H	-*iso*-propoxy
C10(a), (b), and (c)	-H	$-CF_3$
C11(a), (b), and (c)	-H	$-CH_2CF_3$
C12(a), (b), and (c)	-H	$-OCF_3$
C13(a), (b), and (c)	-H	-Cl
C14(a), (b), and (c)	-H	-Br
C15(a), (b), and (c)	-H	-I
C16(a), (b), and (c)	-H	-n-butyl
C17(a), (b), and (c)	-H	-n-propyl
C18(a), (b), and (c)	-Cl	-H
C19(a), (b), and (c)	-Cl	-*tert*-butyl
C20(a), (b), and (c)	-Cl	-*iso*-butyl
C21(a), (b), and (c)	-Cl	-*sec*-butyl
C22(a), (b), and (c)	-Cl	-*iso*-propyl
C23(a), (b), and (c)	-Cl	-n-propyl
C24(a), (b), and (c)	-Cl	-cyclohexyl
C25(a), (b), and (c)	-Cl	-*tert*-butoxy

C26(a), (b), and (c)	-Cl	-*iso*-propoxy
C27(a), (b), and (c)	-Cl	$-CF_3$
C28(a), (b), and (c)	-Cl	$-CH_2CF_3$
C29(a), (b), and (c)	-Cl	$-OCF_3$
C30(a), (b), and (c)	-Cl	-Cl
C31(a), (b), and (c)	-Cl	-Br
C32(a), (b), and (c)	-Cl	-I
C33(a), (b), and (c)	-Cl	-n-butyl
C34(a), (b), and (c)	-Cl	-n-propyl
C35(a), (b), and (c)	-F	-H
C36(a), (b), and (c)	-F	-*tert*-butyl
C37(a), (b), and (c)	-F	-*iso*-butyl
C38(a), (b), and (c)	-F	-*sec*-butyl
C39(a), (b), and (c)	-F	-*iso*-propyl
C40(a), (b), and (c)	-F	-n-propyl
C41(a), (b), and (c)	-F	-cyclohexyl
C42(a), (b), and (c)	-F	-*tert*-butoxy
C43(a), (b), and (c)	-F	-*iso*-propoxy
C44(a), (b), and (c)	-F	$-CF_3$
C45(a), (b), and (c)	-F	$-CH_2CF_3$
C46(a), (b), and (c)	-F	$-OCF_3$
C47(a), (b), and (c)	-F	-Cl
C48(a), (b), and (c)	-F	-Br
C49(a), (b), and (c)	-F	-I
C50(a), (b), and (c)	-F	-n-butyl
C51(a), (b), and (c)	-F	-n-propyl
C52(a), (b), and (c)	$-CH_3$	-H
C53(a), (b), and (c)	$-CH_3$	-*iso*-butyl
C54(a), (b), and (c)	$-CH_3$	-*tert*-butyl
C55(a), (b), and (c)	$-CH_3$	-*sec*-butyl
C56(a), (b), and (c)	$-CH_3$	-*iso*-propyl
C57(a), (b), and (c)	$-CH_3$	-n-propyl
C58(a), (b), and (c)	$-CH_3$	-cyclohexyl
C59(a), (b), and (c)	$-CH_3$	-*tert*-butoxy
C60(a), (b), and (c)	$-CH_3$	-*iso*-propoxy
C61(a), (b), and (c)	$-CH_3$	$-CF_3$
C62(a), (b), and (c)	$-CH_3$	$-CH_2CF_3$
C63(a), (b), and (c)	$-CH_3$	$-OCF_3$
C64(a), (b), and (c)	$-CH_3$	-Cl
C65(a), (b), and (c)	$-CH_3$	-Br
C66(a), (b), and (c)	$-CH_3$	-I
C67(a), (b), and (c)	$-CH_3$	-n-butyl
C68(a), (b), and (c)	$-CH_3$	-n-propyl
C69(a), (b), and (c)	$-CF_3$	-H
C70(a), (b), and (c)	$-CF_3$	-*tert*-butyl
C71(a), (b), and (c)	$-CF_3$	-*iso*-butyl
C72(a), (b), and (c)	$-CF_3$	-*sec*-butyl
C73(a), (b), and (c)	$-CF_3$	-*iso*-propyl

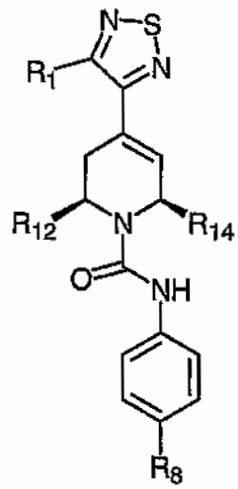
C74(a), (b), and (c)	$-CF_3$	-n-propyl
C75(a), (b), and (c)	$-CF_3$	-cyclohexyl
C76(a), (b), and (c)	$-CF_3$	-*tert*-butoxy
C77(a), (b), and (c)	$-CF_3$	-*iso*-propoxy
C78(a), (b), and (c)	$-CF_3$	$-CF_3$
C79(a), (b), and (c)	$-CF_3$	$-CH_2CF_3$
C80(a), (b), and (c)	$-CF_3$	$-OCF_3$
C81(a), (b), and (c)	$-CF_3$	-Cl
C82(a), (b), and (c)	$-CF_3$	-Br
C83(a), (b), and (c)	$-CF_3$	-I
C84(a), (b), and (c)	$-CF_3$	-n-butyl
C85(a), (b), and (c)	$-CF_3$	-n-propyl
C86(a), (b), and (c)	$-CHF_2$	-*tert*-butyl
C87(a), (b), and (c)	$-CHF_2$	-H
C88(a), (b), and (c)	$-CHF_2$	-*iso*-butyl
C89(a), (b), and (c)	$-CHF_2$	-*sec*-butyl
C90(a), (b), and (c)	$-CHF_2$	-*iso*-propyl
C91(a), (b), and (c)	$-CHF_2$	-n-propyl
C92(a), (b), and (c)	$-CHF_2$	-cyclohexyl
C93(a), (b), and (c)	$-CHF_2$	-*tert*-butoxy
C94(a), (b), and (c)	$-CHF_2$	-*iso*-propoxy
C95(a), (b), and (c)	$-CHF_2$	$-CF_3$
C96(a), (b), and (c)	$-CHF_2$	$-CH_2CF_3$
C97(a), (b), and (c)	$-CHF_2$	$-OCF_3$
C98(a), (b), and (c)	$-CHF_2$	-Cl
C99(a), (b), and (c)	$-CHF_2$	-Br
C100(a), (b), and (c)	$-CHF_2$	-I
C101(a), (b), and (c)	$-CHF_2$	-n-butyl
C102(a), (b), and (c)	$-CHF_2$	-n-propyl
C103(a), (b), and (c)	-OH	-H
C104(a), (b), and (c)	-OH	-*tert*-butyl
C105(a), (b), and (c)	-OH	-*iso*-butyl
C106(a), (b), and (c)	-OH	-*sec*-butyl
C107(a), (b), and (c)	-OH	-*iso*-propyl
C108(a), (b), and (c)	-OH	-n-propyl
C109(a), (b), and (c)	-OH	-cyclohexyl
C110(a), (b), and (c)	-OH	-*tert*-butoxy
C111(a), (b), and (c)	-OH	-*iso*-propoxy
C112(a), (b), and (c)	-OH	$-CF_3$
C113(a), (b), and (c)	-OH	$-CH_2CF_3$
C114(a), (b), and (c)	-OH	$-OCF_3$
C115(a), (b), and (c)	-OH	-Cl
C116(a), (b), and (c)	-OH	-Br
C117(a), (b), and (c)	-OH	-I
C118(a), (b), and (c)	-OH	-n-butyl
C119(a), (b), and (c)	-OH	-n-propyl
C120(a), (b), and (c)	$-NO_2$	-H
C121(a), (b), and (c)	$-NO_2$	-*tert*-butyl

C122(a), (b), and (c)	$-NO_2$	-*iso*-butyl
C123(a), (b), and (c)	$-NO_2$	-*sec*-butyl
C124(a), (b), and (c)	$-NO_2$	-*iso*-propyl
C125(a), (b), and (c)	$-NO_2$	-n-propyl
C126(a), (b), and (c)	$-NO_2$	-cyclohexyl
C127(a), (b), and (c)	$-NO_2$	-*tert*-butoxy
C128(a), (b), and (c)	$-NO_2$	-*iso*-propoxy
C129(a), (b), and (c)	$-NO_2$	$-CF_3$
C130(a), (b), and (c)	$-NO_2$	$-CH_2CF_3$
C131(a), (b), and (c)	$-NO_2$	$-OCF_3$
C132(a), (b), and (c)	$-NO_2$	-Cl
C133(a), (b), and (c)	$-NO_2$	-Br
C134(a), (b), and (c)	$-NO_2$	-I
C135(a), (b), and (c)	$-NO_2$	-n-butyl
C136(a), (b), and (c)	$-NO_2$	-n-propyl
C137(a), (b), and (c)	-CN	-H
C138(a), (b), and (c)	-CN	-*tert*-butyl
C139(a), (b), and (c)	-CN	-*iso*-butyl
C140(a), (b), and (c)	-CN	-*sec*-butyl
C141(a), (b), and (c)	-CN	-*iso*-propyl
C142(a), (b), and (c)	-CN	-n-propyl
C143(a), (b), and (c)	-CN	-cyclohexyl
C144(a), (b), and (c)	-CN	-*tert*-butoxy
C145(a), (b), and (c)	-CN	-*iso*-propoxy
C146(a), (b), and (c)	-CN	$-CF_3$
C147(a), (b), and (c)	-CN	$-CH_2CF_3$
C148(a), (b), and (c)	-CN	$-OCF_3$
C149(a), (b), and (c)	-CN	-Cl
C150(a), (b), and (c)	-CN	-Br
C151(a), (b), and (c)	-CN	-I
C152(a), (b), and (c)	-CN	-n-butyl
C153(a), (b), and (c)	-CN	-n-propyl
C154(a), (b), and (c)	-Br	-H
C155(a), (b), and (c)	-Br	-*tert*-butyl
C156(a), (b), and (c)	-Br	-*iso*-butyl
C157(a), (b), and (c)	-Br	-*sec*-butyl
C158(a), (b), and (c)	-Br	-*iso*-propyl
C159(a), (b), and (c)	-Br	-n-propyl
C160(a), (b), and (c)	-Br	-cyclohexyl
C161(a), (b), and (c)	-Br	-*tert*-butoxy
C162(a), (b), and (c)	-Br	-*iso*-propoxy
C163(a), (b), and (c)	-Br	$-CF_3$
C164(a), (b), and (c)	-Br	$-CH_2CF_3$
C165(a), (b), and (c)	-Br	$-OCF_3$
C166(a), (b), and (c)	-Br	-Cl
C167(a), (b), and (c)	-Br	-Br
C168(a), (b), and (c)	-Br	-I
C169(a), (b), and (c)	-Br	-n-butyl

C170(a), (b), and (c)	-Br	-n-propyl
C171(a), (b), and (c)	-I	-*tert*-butyl
C172(a), (b), and (c)	-I	-H
C173(a), (b), and (c)	-I	-*iso*-butyl
C174(a), (b), and (c)	-I	-*sec*-butyl
C175(a), (b), and (c)	-I	-*iso*-propyl
C176(a), (b), and (c)	-I	-n-propyl
C177(a), (b), and (c)	-I	-cyclohexyl
C178(a), (b), and (c)	-I	-*tert*-butoxy
C179(a), (b), and (c)	-I	-*iso*-propoxy
C180(a), (b), and (c)	-I	$-CF_3$
C181(a), (b), and (c)	-I	$-CH_2CF_3$
C182(a), (b), and (c)	-I	$-OCF_3$
C183(a), (b), and (c)	-I	-Cl
C184(a), (b), and (c)	-I	-Br
C185(a), (b), and (c)	-I	-I
C186(a), (b), and (c)	-I	-n-butyl
C187(a), (b), and (c)	-I	-n-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 4



(Id)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8
D01(a), (b), and (c)	-H	-H
D02(a), (b), and (c)	-H	-*tert*-butyl
D03(a), (b), and (c)	-H	-*iso*-butyl
D04(a), (b), and (c)	-H	-*sec*-butyl
D05(a), (b), and (c)	-H	-*iso*-propyl
D06(a), (b), and (c)	-H	-n-propyl
D07(a), (b), and (c)	-H	-cyclohexyl
D08(a), (b), and (c)	-H	-*tert*-butoxy
D09(a), (b), and (c)	-H	-*iso*-propoxy
D10(a), (b), and (c)	-H	$-CF_3$
D11(a), (b), and (c)	-H	$-CH_2CF_3$
D12(a), (b), and (c)	-H	$-OCF_3$
D13(a), (b), and (c)	-H	-Cl
D14(a), (b), and (c)	-H	-Br
D15(a), (b), and (c)	-H	-I
D16(a), (b), and (c)	-H	-n-butyl
D17(a), (b), and (c)	-H	-n-propyl
D18(a), (b), and (c)	-Cl	-H
D19(a), (b), and (c)	-Cl	-*tert*-butyl
D20(a), (b), and (c)	-Cl	-*iso*-butyl
D21(a), (b), and (c)	-Cl	-*sec*-butyl
D22(a), (b), and (c)	-Cl	-*iso*-propyl
D23(a), (b), and (c)	-Cl	-n-propyl
D24(a), (b), and (c)	-Cl	-cyclohexyl
D25(a), (b), and (c)	-Cl	-*tert*-butoxy
D26(a), (b), and (c)	-Cl	-*iso*-propoxy
D27(a), (b), and (c)	-Cl	$-CF_3$

D28(a), (b), and (c)	-Cl	$-CH_2CF_3$
D29(a), (b), and (c)	-Cl	$-OCF_3$
D30(a), (b), and (c)	-Cl	-Cl
D31(a), (b), and (c)	-Cl	-Br
D32(a), (b), and (c)	-Cl	-I
D33(a), (b), and (c)	-Cl	-n-butyl
D34(a), (b), and (c)	-Cl	-n-propyl
D35(a), (b), and (c)	-F	-H
D36(a), (b), and (c)	-F	-*tert*-butyl
D37(a), (b), and (c)	-F	-*iso*-butyl
D38(a), (b), and (c)	-F	-*sec*-butyl
D39(a), (b), and (c)	-F	-*iso*-propyl
D40(a), (b), and (c)	-F	-n-propyl
D41(a), (b), and (c)	-F	-cyclohexyl
D42(a), (b), and (c)	-F	-*tert*-butoxy
D43(a), (b), and (c)	-F	-*iso*-propoxy
D44(a), (b), and (c)	-F	$-CF_3$
D45(a), (b), and (c)	-F	$-CH_2CF_3$
D46(a), (b), and (c)	-F	$-OCF_3$
D47(a), (b), and (c)	-F	-Cl
D48(a), (b), and (c)	-F	-Br
D49(a), (b), and (c)	-F	-I
D50(a), (b), and (c)	-F	-n-butyl
D51(a), (b), and (c)	-F	-n-propyl
D52(a), (b), and (c)	$-CH_3$	-H
D53(a), (b), and (c)	$-CH_3$	-*iso*-butyl
D54(a), (b), and (c)	$-CH_3$	-*tert*-butyl
D55(a), (b), and (c)	$-CH_3$	-*sec*-butyl
D56(a), (b), and (c)	$-CH_3$	-*iso*-propyl
D57(a), (b), and (c)	$-CH_3$	-n-propyl
D58(a), (b), and (c)	$-CH_3$	-cyclohexyl
D59(a), (b), and (c)	$-CH_3$	-*tert*-butoxy
D60(a), (b), and (c)	$-CH_3$	-*iso*-propoxy
D61(a), (b), and (c)	$-CH_3$	$-CF_3$
D62(a), (b), and (c)	$-CH_3$	$-CH_2CF_3$
D63(a), (b), and (c)	$-CH_3$	$-OCF_3$
D64(a), (b), and (c)	$-CH_3$	-Cl
D65(a), (b), and (c)	$-CH_3$	-Br
D66(a), (b), and (c)	$-CH_3$	-I
D67(a), (b), and (c)	$-CH_3$	-n-butyl
D68(a), (b), and (c)	$-CH_3$	-n-propyl
D69(a), (b), and (c)	$-CF_3$	-H
D70(a), (b), and (c)	$-CF_3$	-*tert*-butyl
D71(a), (b), and (c)	$-CF_3$	-*iso*-butyl
D72(a), (b), and (c)	$-CF_3$	-*sec*-butyl
D73(a), (b), and (c)	$-CF_3$	-*iso*-propyl
D74(a), (b), and (c)	$-CF_3$	-n-propyl
D75(a), (b), and (c)	$-CF_3$	-cyclohexyl

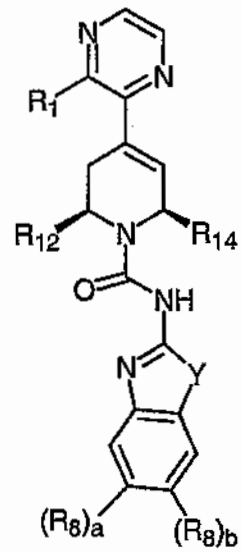
D76(a), (b), and (c)	$-CF_3$	-*tert*-butoxy
D77(a), (b), and (c)	$-CF_3$	-*iso*-propoxy
D78(a), (b), and (c)	$-CF_3$	$-CF_3$
D79(a), (b), and (c)	$-CF_3$	$-CH_2CF_3$
D80(a), (b), and (c)	$-CF_3$	$-OCF_3$
D81(a), (b), and (c)	$-CF_3$	-Cl
D82(a), (b), and (c)	$-CF_3$	-Br
D83(a), (b), and (c)	$-CF_3$	-I
D84(a), (b), and (c)	$-CF_3$	-n-butyl
D85(a), (b), and (c)	$-CF_3$	-n-propyl
D86(a), (b), and (c)	$-CHF_2$	-*tert*-butyl
D87(a), (b), and (c)	$-CHF_2$	-H
D88(a), (b), and (c)	$-CHF_2$	-*iso*-butyl
D89(a), (b), and (c)	$-CHF_2$	-*sec*-butyl
D90(a), (b), and (c)	$-CHF_2$	-*iso*-propyl
D91(a), (b), and (c)	$-CHF_2$	-n-propyl
D92(a), (b), and (c)	$-CHF_2$	-cyclohexyl
D93(a), (b), and (c)	$-CHF_2$	-*tert*-butoxy
D94(a), (b), and (c)	$-CHF_2$	-*iso*-propoxy
D95(a), (b), and (c)	$-CHF_2$	$-CF_3$
D96(a), (b), and (c)	$-CHF_2$	$-CH_2CF_3$
D97(a), (b), and (c)	$-CHF_2$	$-OCF_3$
D98(a), (b), and (c)	$-CHF_2$	-Cl
D99(a), (b), and (c)	$-CHF_2$	-Br
D100(a), (b), and (c)	$-CHF_2$	-I
D101(a), (b), and (c)	$-CHF_2$	-n-butyl
D102(a), (b), and (c)	$-CHF_2$	-n-propyl
D103(a), (b), and (c)	-OH	-H
D104(a), (b), and (c)	-OH	-*tert*-butyl
D105(a), (b), and (c)	-OH	-*iso*-butyl
D106(a), (b), and (c)	-OH	-*sec*-butyl
D107(a), (b), and (c)	-OH	-*iso*-propyl
D108(a), (b), and (c)	-OH	-n-propyl
D109(a), (b), and (c)	-OH	-cyclohexyl
D110(a), (b), and (c)	-OH	-*tert*-butoxy
D111(a), (b), and (c)	-OH	-*iso*-propoxy
D112(a), (b), and (c)	-OH	$-CF_3$
D113(a), (b), and (c)	-OH	$-CH_2CF_3$
D114(a), (b), and (c)	-OH	$-OCF_3$
D115(a), (b), and (c)	-OH	-Cl
D116(a), (b), and (c)	-OH	-Br
D117(a), (b), and (c)	-OH	-I
D118(a), (b), and (c)	-OH	-n-butyl
D119(a), (b), and (c)	-OH	-n-propyl
D120(a), (b), and (c)	$-NO_2$	-H
D121(a), (b), and (c)	$-NO_2$	-*tert*-butyl
D122(a), (b), and (c)	$-NO_2$	-*iso*-butyl
D123(a), (b), and (c)	$-NO_2$	-*sec*-butyl

D124(a), (b), and (c)	$-NO_2$	-*iso*-propyl
D125(a), (b), and (c)	$-NO_2$	-n-propyl
D126(a), (b), and (c)	$-NO_2$	-cyclohexyl
D127(a), (b), and (c)	$-NO_2$	-*tert*-butoxy
D128(a), (b), and (c)	$-NO_2$	-*iso*-propoxy
D129(a), (b), and (c)	$-NO_2$	$-CF_3$
D130(a), (b), and (c)	$-NO_2$	$-CH_2CF_3$
D131(a), (b), and (c)	$-NO_2$	$-OCF_3$
D132(a), (b), and (c)	$-NO_2$	-Cl
D133(a), (b), and (c)	$-NO_2$	-Br
D134(a), (b), and (c)	$-NO_2$	-I
D135(a), (b), and (c)	$-NO_2$	-n-butyl
D136(a), (b), and (c)	$-NO_2$	-n-propyl
D137(a), (b), and (c)	-CN	-H
D138(a), (b), and (c)	-CN	-*tert*-butyl
D139(a), (b), and (c)	-CN	-*iso*-butyl
D140(a), (b), and (c)	-CN	-*sec*-butyl
D141(a), (b), and (c)	-CN	-*iso*-propyl
D142(a), (b), and (c)	-CN	-n-propyl
D143(a), (b), and (c)	-CN	-cyclohexyl
D144(a), (b), and (c)	-CN	-*tert*-butoxy
D145(a), (b), and (c)	-CN	-*iso*-propoxy
D146(a), (b), and (c)	-CN	$-CF_3$
D147(a), (b), and (c)	-CN	$-CH_2CF_3$
D148(a), (b), and (c)	-CN	$-OCF_3$
D149(a), (b), and (c)	-CN	-Cl
D150(a), (b), and (c)	-CN	-Br
D151(a), (b), and (c)	-CN	-I
D152(a), (b), and (c)	-CN	-n-butyl
D153(a), (b), and (c)	-CN	-n-propyl
D154(a), (b), and (c)	-Br	-H
D155(a), (b), and (c)	-Br	-*tert*-butyl
D156(a), (b), and (c)	-Br	-*iso*-butyl
D157(a), (b), and (c)	-Br	-*sec*-butyl
D158(a), (b), and (c)	-Br	-*iso*-propyl
D159(a), (b), and (c)	-Br	-n-propyl
D160(a), (b), and (c)	-Br	-cyclohexyl
D161(a), (b), and (c)	-Br	-*tert*-butoxy
D162(a), (b), and (c)	-Br	-*iso*-propoxy
D163(a), (b), and (c)	-Br	$-CF_3$
D164(a), (b), and (c)	-Br	$-CH_2CF_3$
D165(a), (b), and (c)	-Br	$-OCF_3$
D166(a), (b), and (c)	-Br	-Cl
D167(a), (b), and (c)	-Br	-Br
D168(a), (b), and (c)	-Br	-I
D169(a), (b), and (c)	-Br	-n-butyl
D170(a), (b), and (c)	-Br	-n-propyl
D171(a), (b), and (c)	-I	-*tert*-butyl

D172(a), (b), and (c)	-I	-H
D173(a), (b), and (c)	-I	-*iso*-butyl
D174(a), (b), and (c)	-I	-*sec*-butyl
D175(a), (b), and (c)	-I	-*iso*-propyl
D176(a), (b), and (c)	-I	-n-propyl
D177(a), (b), and (c)	-I	-cyclohexyl
D178(a), (b), and (c)	-I	-*tert*-butoxy
D179(a), (b), and (c)	-I	-*iso*-propoxy
D180(a), (b), and (c)	-I	$-CF_3$
D181(a), (b), and (c)	-I	$-CH_2CF_3$
D182(a), (b), and (c)	-I	$-OCF_3$
D183(a), (b), and (c)	-I	-Cl
D184(a), (b), and (c)	-I	-Br
D185(a), (b), and (c)	-I	-I
D186(a), (b), and (c)	-I	-n-butyl
D187(a), (b), and (c)	-I	-n-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 5



(Ie)

and pharmaceutically acceptable salts thereof, where:

Compound	Y	R_1	$(R_8)_a$	$(R_8)_b$
E01(a), (b), and (c)	S	-H	-Cl	-H
E02(a), (b), and (c)	S	-H	-Br	-H
E03(a), (b), and (c)	S	-H	-F	-H
E04(a), (b), and (c)	S	-H	$-CH_3$	-H
E05(a), (b), and (c)	S	-H	$-CF_3$	-H
E06(a), (b), and (c)	S	-H	$-OCH_3$	-H
E07(a), (b), and (c)	S	-H	$-OCH_2CH_3$	-H
E08(a), (b), and (c)	S	-H	$-OCF_3$	-H
E09(a), (b), and (c)	S	-H	-*tert*-butyl	-H
E10(a), (b), and (c)	S	-H	-*iso*-propyl	-H
E11(a), (b), and (c)	S	-H	$-CH_3$	$-CH_3$
E12(a), (b), and (c)	S	-H	-H	-H
E13(a), (b), and (c)	S	-H	-H	-Cl
E14(a), (b), and (c)	S	-H	-H	-Br
E15(a), (b), and (c)	S	-H	-H	-F
E16(a), (b), and (c)	S	-H	-H	$-CH_3$
E17(a), (b), and (c)	S	-H	-H	$-CF_3$
E18(a), (b), and (c)	S	-H	-H	$-OCH_3$
E19(a), (b), and (c)	S	-H	-H	$-OCH_2CH_3$
E20(a), (b), and (c)	S	-H	-H	$-OCF_3$
E21(a), (b), and (c)	S	-H	-H	-*tert*-butyl
E22(a), (b), and (c)	S	-H	-H	-*iso*-propyl
E23(a), (b), and (c)	S	-Cl	-Cl	-H
E24(a), (b), and (c)	S	-Cl	-Br	-H
E25(a), (b), and (c)	S	-Cl	-F	-H

E26(a), (b), and (c)	S	-Cl	$-CH_3$	-H
E27(a), (b), and (c)	S	-Cl	$-CF_3$	-H
E28(a), (b), and (c)	S	-Cl	$-OCH_3$	-H
E29(a), (b), and (c)	S	-Cl	$-OCH_2CH_3$	-H
E30(a), (b), and (c)	S	-Cl	$-OCF_3$	-H
E31(a), (b), and (c)	S	-Cl	*-tert*-butyl	-H
E32(a), (b), and (c)	S	-Cl	*-iso*-propyl	-H
E33(a), (b), and (c)	S	-Cl	$-CH_3$	$-CH_3$
E34(a), (b), and (c)	S	-Cl	-H	-H
E35(a), (b), and (c)	S	-Cl	-H	-Cl
E36(a), (b), and (c)	S	-Cl	-H	-Br
E37(a), (b), and (c)	S	-Cl	-H	-F
E38(a), (b), and (c)	S	-Cl	-H	$-CH_3$
E39(a), (b), and (c)	S	-Cl	-H	$-CF_3$
E40(a), (b), and (c)	S	-Cl	-H	$-OCH_3$
E41(a), (b), and (c)	S	-Cl	-H	$-OCH_2CH_3$
E42(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
E43(a), (b), and (c)	S	-Cl	-H	*-tert*-butyl
E44(a), (b), and (c)	S	-Cl	-H	*-iso*-propyl
E45(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
E46(a), (b), and (c)	S	-Cl	-H	*-tert*-butyl
E47(a), (b), and (c)	S	-Cl	-H	*-iso*-propyl
E48(a), (b), and (c)	S	$-CH_3$	-Cl	-H
E49(a), (b), and (c)	S	$-CH_3$	-Br	-H
E50(a), (b), and (c)	S	$-CH_3$	-F	-H
E51(a), (b), and (c)	S	$-CH_3$	$-CH_3$	-H
E52(a), (b), and (c)	S	$-CH_3$	$-CF_3$	-H
E53(a), (b), and (c)	S	$-CH_3$	$-OCH_3$	-H
E54(a), (b), and (c)	S	$-CH_3$	$-OCH_2CH_3$	-H
E55(a), (b), and (c)	S	$-CH_3$	$-OCF_3$	-H
E56(a), (b), and (c)	S	$-CH_3$	*-tert*-butyl	-H
E57(a), (b), and (c)	S	$-CH_3$	*-iso*-propyl	-H
E58(a), (b), and (c)	S	$-CH_3$	$-CH_3$	$-CH_3$
E59(a), (b), and (c)	S	$-CH_3$	-H	-H
E60(a), (b), and (c)	S	$-CH_3$	-H	-Cl
E61(a), (b), and (c)	S	$-CH_3$	-H	-Br
E62(a), (b), and (c)	S	$-CH_3$	-H	-F
E63(a), (b), and (c)	S	$-CH_3$	-H	$-CH_3$
E64(a), (b), and (c)	S	$-CH_3$	-H	$-CF_3$
E65(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_3$
E66(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_2CH_3$
E67(a), (b), and (c)	S	$-CH_3$	-H	$-OCF_3$
E68(a), (b), and (c)	S	$-CH_3$	-H	*-tert*-butyl
E69(a), (b), and (c)	S	$-CH_3$	-H	*-iso*-propyl
E70(a), (b), and (c)	S	$-CF_3$	-Cl	-H
E71(a), (b), and (c)	S	$-CF_3$	-Br	-H
E72(a), (b), and (c)	S	$-CF_3$	-F	-H
E73(a), (b), and (c)	S	$-CF_3$	$-CH_3$	-H

E74(a), (b), and (c)	S	$-CF_3$	$-CF_3$	-H
E75(a), (b), and (c)	S	$-CF_3$	$-OCH_3$	-H
E76(a), (b), and (c)	S	$-CF_3$	$-OCH_2CH_3$	-H
E77(a), (b), and (c)	S	$-CF_3$	$-OCF_3$	-H
E78(a), (b), and (c)	S	$-CF_3$	-*tert*-butyl	-H
E79(a), (b), and (c)	S	$-CF_3$	-*iso*-propyl	-H
E80(a), (b), and (c)	S	$-CF_3$	$-CH_3$	$-CH_3$
E81(a), (b), and (c)	S	$-CF_3$	-H	-H
E82(a), (b), and (c)	S	$-CF_3$	-H	-Cl
E83(a), (b), and (c)	S	$-CF_3$	-H	-Br
E84(a), (b), and (c)	S	$-CF_3$	-H	-F
E85(a), (b), and (c)	S	$-CF_3$	-H	$-CH_3$
E86(a), (b), and (c)	S	$-CF_3$	-H	$-CF_3$
E87(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_3$
E88(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_2CH_3$
E89(a), (b), and (c)	S	$-CF_3$	-H	$-OCF_3$
E90(a), (b), and (c)	S	$-CF_3$	-H	-*tert*-butyl
E91(a), (b), and (c)	S	$-CF_3$	-H	-*iso*-propyl
E92(a), (b), and (c)	S	$-CHF_2$	-Cl	-H
E93(a), (b), and (c)	S	$-CHF_2$	-Br	-H
E94(a), (b), and (c)	S	$-CHF_2$	-F	-H
E95(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	-H
E96(a), (b), and (c)	S	$-CHF_2$	$-CF_3$	-H
E97(a), (b), and (c)	S	$-CHF_2$	$-OCH_3$	-H
E98(a), (b), and (c)	S	$-CHF_2$	$-OCH_2CH_3$	-H
E99(a), (b), and (c)	S	$-CHF_2$	$-OCF_3$	-H
E100(a), (b), and (c)	S	$-CHF_2$	-*tert*-butyl	-H
E101(a), (b), and (c)	S	$-CHF_2$	-*iso*-propyl	-H
E102(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	$-CH_3$
E103(a), (b), and (c)	S	$-CHF_2$	-H	-H
E104(a), (b), and (c)	S	$-CHF_2$	-H	-Cl
E105(a), (b), and (c)	S	$-CHF_2$	-H	-Br
E106(a), (b), and (c)	S	$-CHF_2$	-H	-F
E107(a), (b), and (c)	S	$-CHF_2$	-H	$-CH_3$
E108(a), (b), and (c)	S	$-CHF_2$	-H	$-CF_3$
E109(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_3$
E110(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_2CH_3$
E111(a), (b), and (c)	S	$-CHF_2$	-H	$-OCF_3$
E112(a), (b), and (c)	S	$-CHF_2$	-H	-*tert*-butyl
E113(a), (b), and (c)	S	$-CHF_2$	-H	-*iso*-propyl
E114(a), (b), and (c)	S	-OH	-Cl	-H
E115(a), (b), and (c)	S	-OH	-Br	-H
E116(a), (b), and (c)	S	-OH	-F	-H
E117(a), (b), and (c)	S	-OH	$-CH_3$	-H
E118(a), (b), and (c)	S	-OH	$-CF_3$	-H
E119(a), (b), and (c)	S	-OH	$-OCH_3$	-H
E120(a), (b), and (c)	S	-OH	$-OCH_2CH_3$	-H
E121(a), (b), and (c)	S	-OH	$-OCF_3$	-H

E122(a), (b), and (c)	S	-OH	-*tert*-butyl	-H
E123(a), (b), and (c)	S	-OH	-*iso*-propyl	-H
E124(a), (b), and (c)	S	-OH	$-CH_3$	$-CH_3$
E125(a), (b), and (c)	S	-OH	-H	-H
E126(a), (b), and (c)	S	-OH	-H	-Cl
E127(a), (b), and (c)	S	-OH	-H	-Br
E128(a), (b), and (c)	S	-OH	-H	-F
E129(a), (b), and (c)	S	-OH	-H	$-CH_3$
E130(a), (b), and (c)	S	-OH	-H	$-CF_3$
E131(a), (b), and (c)	S	-OH	-H	$-OCH_3$
E132(a), (b), and (c)	S	-OH	-H	$-OCH_2CH_3$
E133(a), (b), and (c)	S	-OH	-H	$-OCF_3$
E134(a), (b), and (c)	S	-OH	-H	-*tert*-butyl
E135(a), (b), and (c)	S	-OH	-H	-*iso*-propyl
E136(a), (b), and (c)	S	$-NO_2$	-Cl	-H
E137(a), (b), and (c)	S	$-NO_2$	-Br	-H
E138(a), (b), and (c)	S	$-NO_2$	-F	-H
E139(a), (b), and (c)	S	$-NO_2$	$-CH_3$	-H
E140(a), (b), and (c)	S	$-NO_2$	$-CF_3$	-H
E141(a), (b), and (c)	S	$-NO_2$	$-OCH_3$	-H
E142(a), (b), and (c)	S	$-NO_2$	$-OCH_2CH_3$	-H
E143(a), (b), and (c)	S	$-NO_2$	$-OCF_3$	-H
E144(a), (b), and (c)	S	$-NO_2$	-*tert*-butyl	-H
E145(a), (b), and (c)	S	$-NO_2$	-*iso*-propyl	-H
E146(a), (b), and (c)	S	$-NO_2$	$-CH_3$	$-CH_3$
E147(a), (b), and (c)	S	$-NO_2$	-H	-H
E148(a), (b), and (c)	S	$-NO_2$	-H	-Cl
E149(a), (b), and (c)	S	$-NO_2$	-H	-Br
E150(a), (b), and (c)	S	$-NO_2$	-H	-F
E151(a), (b), and (c)	S	$-NO_2$	-H	$-CH_3$
E152(a), (b), and (c)	S	$-NO_2$	-H	$-CF_3$
E153(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_3$
E154(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_2CH_3$
E155(a), (b), and (c)	S	$-NO_2$	-H	$-OCF_3$
E156(a), (b), and (c)	S	$-NO_2$	-H	-*tert*-butyl
E157(a), (b), and (c)	S	$-NO_2$	-H	-*iso*-propyl
E158(a), (b), and (c)	S	-CN	-Br	-H
E159(a), (b), and (c)	S	-CN	-Cl	-H
E160(a), (b), and (c)	S	-CN	-F	-H
E161(a), (b), and (c)	S	-CN	$-CH_3$	-H
E162(a), (b), and (c)	S	-CN	$-CF_3$	-H
E163(a), (b), and (c)	S	-CN	$-OCH_3$	-H
E164(a), (b), and (c)	S	-CN	$-OCH_2CH_3$	-H
E165(a), (b), and (c)	S	-CN	$-OCF_3$	-H
E166(a), (b), and (c)	S	-CN	-*tert*-butyl	-H
E167(a), (b), and (c)	S	-CN	-*iso*-propyl	-H
E168(a), (b), and (c)	S	-CN	$-CH_3$	$-CH_3$
E169(a), (b), and (c)	S	-CN	-H	-H

E170(a), (b), and (c)	S	-CN	-H	-Cl
E171(a), (b), and (c)	S	-CN	-H	-Br
E172(a), (b), and (c)	S	-CN	-H	-F
E173(a), (b), and (c)	S	-CN	-H	$-CH_3$
E174(a), (b), and (c)	S	-CN	-H	$-CF_3$
E175(a), (b), and (c)	S	-CN	-H	$-OCH_3$
E176(a), (b), and (c)	S	-CN	-H	$-OCH_2CH_3$
E177(a), (b), and (c)	S	-CN	-H	$-OCF_3$
E178(a), (b), and (c)	S	-CN	-H	*-tert*-butyl
E179(a), (b), and (c)	S	-CN	-H	*-iso*-propyl
E180(a), (b), and (c)	S	-Br	-Br	-H
E181(a), (b), and (c)	S	-Br	-Cl	-H
E182(a), (b), and (c)	S	-Br	-F	-H
E183(a), (b), and (c)	S	-Br	$-CH_3$	-H
E184(a), (b), and (c)	S	-Br	$-CF_3$	-H
E185(a), (b), and (c)	S	-Br	$-OCH_3$	-H
E186(a), (b), and (c)	S	-Br	$-OCH_2CH_3$	-H
E187(a), (b), and (c)	S	-Br	$-OCF_3$	-H
E188(a), (b), and (c)	S	-Br	*-tert*-butyl	-H
E189(a), (b), and (c)	S	-Br	*-iso*-propyl	-H
E190(a), (b), and (c)	S	-Br	$-CH_3$	$-CH_3$
E191(a), (b), and (c)	S	-Br	-H	-H
E192(a), (b), and (c)	S	-Br	-H	-Cl
E193(a), (b), and (c)	S	-Br	-H	-Br
E194(a), (b), and (c)	S	-Br	-H	-F
E195(a), (b), and (c)	S	-Br	-H	$-CH_3$
E196(a), (b), and (c)	S	-Br	-H	$-CF_3$
E197(a), (b), and (c)	S	-Br	-H	$-OCH_3$
E198(a), (b), and (c)	S	-Br	-H	$-OCH_2CH_3$
E199(a), (b), and (c)	S	-Br	-H	$-OCF_3$
E200(a), (b), and (c)	S	-Br	-H	*-tert*-butyl
E201(a), (b), and (c)	S	-Br	-H	*-iso*-propyl
E202(a), (b), and (c)	S	-I	-Cl	-H
E203(a), (b), and (c)	S	-I	-Br	-H
E204(a), (b), and (c)	S	-I	-F	-H
E205(a), (b), and (c)	S	-I	$-CH_3$	-H
E206(a), (b), and (c)	S	-I	$-CF_3$	-H
E207(a), (b), and (c)	S	-I	$-OCH_3$	-H
E208(a), (b), and (c)	S	-I	$-OCH_2CH_3$	-H
E209(a), (b), and (c)	S	-I	$-OCF_3$	-H
E210(a), (b), and (c)	S	-I	*-tert*-butyl	-H
E211(a), (b), and (c)	S	-I	*-iso*-propyl	-H
E212(a), (b), and (c)	S	-I	$-CH_3$	$-CH_3$
E213(a), (b), and (c)	S	-I	-H	-H
E214(a), (b), and (c)	S	-I	-H	-Cl
E215(a), (b), and (c)	S	-I	-H	-Br
E216(a), (b), and (c)	S	-I	-H	-F
E217(a), (b), and (c)	S	-I	-H	$-CH_3$

E218(a), (b), and (c)	S	-I	-H	$-CF_3$
E219(a), (b), and (c)	S	-I	-H	$-OCH_3$
E220(a), (b), and (c)	S	-I	-H	$-OCH_2CH_3$
E221(a), (b), and (c)	S	-I	-H	$-OCF_3$
E222(a), (b), and (c)	S	-I	-H	-*tert*-butyl
E223(a), (b), and (c)	S	-I	-H	-*iso*-propyl
E224(a), (b), and (c)	O	-H	-Cl	-H
E225(a), (b), and (c)	O	-H	-Br	-H
E226(a), (b), and (c)	O	-H	-F	-H
E227(a), (b), and (c)	O	-H	$-CH_3$	-H
E228(a), (b), and (c)	O	-H	$-CF_3$	-H
E229(a), (b), and (c)	O	-H	$-OCH_3$	-H
E230(a), (b), and (c)	O	-H	$-OCH_2CH_3$	-H
E231(a), (b), and (c)	O	-H	$-OCF_3$	-H
E232(a), (b), and (c)	O	-H	-*tert*-butyl	-H
E233(a), (b), and (c)	O	-H	-*iso*-propyl	-H
E234(a), (b), and (c)	O	-H	$-CH_3$	$-CH_3$
E235(a), (b), and (c)	O	-H	-H	-H
E236(a), (b), and (c)	O	-H	-H	-Cl
E237(a), (b), and (c)	O	-H	-H	-Br
E238(a), (b), and (c)	O	-H	-H	-F
E239(a), (b), and (c)	O	-H	-H	$-CH_3$
E240(a), (b), and (c)	O	-H	-H	$-CF_3$
E241(a), (b), and (c)	O	-H	-H	$-OCH_3$
E242(a), (b), and (c)	O	-H	-H	$-OCH_2CH_3$
E243(a), (b), and (c)	O	-H	-H	$-OCF_3$
E244(a), (b), and (c)	O	-H	-H	-*tert*-butyl
E245(a), (b), and (c)	O	-H	-H	-*iso*-propyl
E246(a), (b), and (c)	O	-Cl	-Cl	-H
E247(a), (b), and (c)	O	-Cl	-Br	-H
E248(a), (b), and (c)	O	-Cl	-F	-H
E249(a), (b), and (c)	O	-Cl	$-CH_3$	-H
E250(a), (b), and (c)	O	-Cl	$-CF_3$	-H
E251(a), (b), and (c)	O	-Cl	$-OCH_3$	-H
E252(a), (b), and (c)	O	-Cl	$-OCH_2CH_3$	-H
E253(a), (b), and (c)	O	-Cl	$-OCF_3$	-H
E254(a), (b), and (c)	O	-Cl	-*tert*-butyl	-H
E255(a), (b), and (c)	O	-Cl	-*iso*-propyl	-H
E256(a), (b), and (c)	O	-Cl	$-CH_3$	$-CH_3$
E257(a), (b), and (c)	O	-Cl	-H	-H
E258(a), (b), and (c)	O	-Cl	-H	$-CH_3$
E259(a), (b), and (c)	O	-Cl	-H	-Cl
E260(a), (b), and (c)	O	-Cl	-H	-Br
E261(a), (b), and (c)	O	-Cl	-H	-F
E262(a), (b), and (c)	O	-Cl	-H	$-CF_3$
E263(a), (b), and (c)	O	-Cl	-H	$-OCH_3$
E264(a), (b), and (c)	O	-Cl	-H	$-OCH_2CH_3$
E265(a), (b), and (c)	O	-Cl	-H	$-OCF_3$

E266(a), (b), and (c)	O	-Cl	-H	-*tert*-butyl
E267(a), (b), and (c)	O	-Cl	-H	-*iso*-propyl
E268(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
E269(a), (b), and (c)	O	-Cl	-H	-*tert*-butyl
E270(a), (b), and (c)	O	-Cl	-H	-*iso*-propyl
E271(a), (b), and (c)	O	$-CH_3$	-Cl	-H
E272(a), (b), and (c)	O	$-CH_3$	-Br	-H
E273(a), (b), and (c)	O	$-CH_3$	-F	-H
E274(a), (b), and (c)	O	$-CH_3$	$-CH_3$	-H
E275(a), (b), and (c)	O	$-CH_3$	$-CF_3$	-H
E276(a), (b), and (c)	O	$-CH_3$	$-OCH_3$	-H
E277(a), (b), and (c)	O	$-CH_3$	$-OCH_2CH_3$	-H
E278(a), (b), and (c)	O	$-CH_3$	$-OCF_3$	-H
E279(a), (b), and (c)	O	$-CH_3$	-*tert*-butyl	-H
E280(a), (b), and (c)	O	$-CH_3$	-*iso*-propyl	-H
E281(a), (b), and (c)	O	$-CH_3$	$-CH_3$	$-CH_3$
E282(a), (b), and (c)	O	$-CH_3$	-H	-H
E283(a), (b), and (c)	O	$-CH_3$	-H	-Cl
E284(a), (b), and (c)	O	$-CH_3$	-H	-Br
E285(a), (b), and (c)	O	$-CH_3$	-H	-F
E286(a), (b), and (c)	O	$-CH_3$	-H	$-CH_3$
E287(a), (b), and (c)	O	$-CH_3$	-H	$-CF_3$
E288(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_3$
E289(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_2CH_3$
E290(a), (b), and (c)	O	$-CH_3$	-H	$-OCF_3$
E291(a), (b), and (c)	O	$-CH_3$	-H	-*tert*-butyl
E292(a), (b), and (c)	O	$-CH_3$	-H	-*iso*-propyl
E293(a), (b), and (c)	O	$-CF_3$	-Cl	-H
E294(a), (b), and (c)	O	$-CF_3$	-Br	-H
E295(a), (b), and (c)	O	$-CF_3$	-F	-H
E296(a), (b), and (c)	O	$-CF_3$	$-CH_3$	-H
E297(a), (b), and (c)	O	$-CF_3$	$-CF_3$	-H
E298(a), (b), and (c)	O	$-CF_3$	$-OCH_3$	-H
E299(a), (b), and (c)	O	$-CF_3$	$-OCH_2CH_3$	-H
E300(a), (b), and (c)	O	$-CF_3$	$-OCF_3$	-H
E301(a), (b), and (c)	O	$-CF_3$	-*tert*-butyl	-H
E302(a), (b), and (c)	O	$-CF_3$	-*iso*-propyl	-H
E303(a), (b), and (c)	O	$-CF_3$	$-CH_3$	$-CH_3$
E304(a), (b), and (c)	O	$-CF_3$	-H	-H
E305(a), (b), and (c)	O	$-CF_3$	-H	-Cl
E306(a), (b), and (c)	O	$-CF_3$	-H	-Br
E307(a), (b), and (c)	O	$-CF_3$	-H	-F
E308(a), (b), and (c)	O	$-CF_3$	-H	$-CH_3$
E309(a), (b), and (c)	O	$-CF_3$	-H	$-CF_3$
E310(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_3$
E311(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_2CH_3$
E312(a), (b), and (c)	O	$-CF_3$	-H	$-OCF_3$
E313(a), (b), and (c)	O	$-CF_3$	-H	-*tert*-butyl

E314(a), (b), and (c)	O	$-CF_3$	-H	-*iso*-propyl
E315(a), (b), and (c)	O	$-CHF_2$	-Cl	-H
E316(a), (b), and (c)	O	$-CHF_2$	-Br	-H
E317(a), (b), and (c)	O	$-CHF_2$	-F	-H
E318(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	-H
E319(a), (b), and (c)	O	$-CHF_2$	$-CF_3$	-H
E320(a), (b), and (c)	O	$-CHF_2$	$-OCH_3$	-H
E321(a), (b), and (c)	O	$-CHF_2$	$-OCH_2CH_3$	-H
E322(a), (b), and (c)	O	$-CHF_2$	$-OCF_3$	-H
E323(a), (b), and (c)	O	$-CHF_2$	-*tert*-butyl	-H
E324(a), (b), and (c)	O	$-CHF_2$	-*iso*-propyl	-H
E325(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	$-CH_3$
E326(a), (b), and (c)	O	$-CHF_2$	-H	-H
E327(a), (b), and (c)	O	$-CHF_2$	-H	-Cl
E328(a), (b), and (c)	O	$-CHF_2$	-H	-Br
E329(a), (b), and (c)	O	$-CHF_2$	-H	-F
E330(a), (b), and (c)	O	$-CHF_2$	-H	$-CH_3$
E331(a), (b), and (c)	O	$-CHF_2$	-H	$-CF_3$
E332(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_3$
E333(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_2CH_3$
E334(a), (b), and (c)	O	$-CHF_2$	-H	$-OCF_3$
E335(a), (b), and (c)	O	$-CHF_2$	-H	-*tert*-butyl
E336(a), (b), and (c)	O	$-CHF_2$	-H	-*iso*-propyl
E337(a), (b), and (c)	O	-OH	-Cl	-H
E338(a), (b), and (c)	O	-OH	-Br	-H
E339(a), (b), and (c)	O	-OH	-F	-H
E340(a), (b), and (c)	O	-OH	$-CH_3$	-H
E341(a), (b), and (c)	O	-OH	$-CF_3$	-H
E342(a), (b), and (c)	O	-OH	$-OCH_3$	-H
E343(a), (b), and (c)	O	-OH	$-OCH_2CH_3$	-H
E344(a), (b), and (c)	O	-OH	$-OCF_3$	-H
E345(a), (b), and (c)	O	-OH	-*tert*-butyl	-H
E346(a), (b), and (c)	O	-OH	-*iso*-propyl	-H
E347(a), (b), and (c)	O	-OH	$-CH_3$	$-CH_3$
E348(a), (b), and (c)	O	-OH	-H	-H
E349(a), (b), and (c)	O	-OH	-H	-Cl
E350(a), (b), and (c)	O	-OH	-H	-Br
E351(a), (b), and (c)	O	-OH	-H	-F
E352(a), (b), and (c)	O	-OH	-H	$-CH_3$
E353(a), (b), and (c)	O	-OH	-H	$-CF_3$
E354(a), (b), and (c)	O	-OH	-H	$-OCH_3$
E355(a), (b), and (c)	O	-OH	-H	$-OCH_2CH_3$
E356(a), (b), and (c)	O	-OH	-H	$-OCF_3$
E357(a), (b), and (c)	O	-OH	-H	-*tert*-butyl
E358(a), (b), and (c)	O	-OH	-H	-*iso*-propyl
E359(a), (b), and (c)	O	$-NO_2$	-Cl	-H
E360(a), (b), and (c)	O	$-NO_2$	-Br	-H
E361(a), (b), and (c)	O	$-NO_2$	-F	-H

E362(a), (b), and (c)	O	$-NO_2$	$-CH_3$	-H
E363(a), (b), and (c)	O	$-NO_2$	$-CF_3$	-H
E364(a), (b), and (c)	O	$-NO_2$	$-OCH_3$	-H
E365(a), (b), and (c)	O	$-NO_2$	$-OCH_2CH_3$	-H
E366(a), (b), and (c)	O	$-NO_2$	$-OCF_3$	-H
E367(a), (b), and (c)	O	$-NO_2$	*-tert*-butyl	-H
E368(a), (b), and (c)	O	$-NO_2$	*-iso*-propyl	-H
E369(a), (b), and (c)	O	$-NO_2$	$-CH_3$	$-CH_3$
E370(a), (b), and (c)	O	$-NO_2$	-H	-H
E371(a), (b), and (c)	O	$-NO_2$	-H	-Cl
E372(a), (b), and (c)	O	$-NO_2$	-H	-Br
E373(a), (b), and (c)	O	$-NO_2$	-H	-F
E374(a), (b), and (c)	O	$-NO_2$	-H	$-CH_3$
E375(a), (b), and (c)	O	$-NO_2$	-H	$-CF_3$
E376(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_3$
E377(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_2CH_3$
E378(a), (b), and (c)	O	$-NO_2$	-H	$-OCF_3$
E379(a), (b), and (c)	O	$-NO_2$	-H	*-tert*-butyl
E380(a), (b), and (c)	O	$-NO_2$	-H	*-iso*-propyl
E381(a), (b), and (c)	O	-CN	-Br	-H
E382(a), (b), and (c)	O	-CN	-Cl	-H
E383(a), (b), and (c)	O	-CN	-F	-H
E384(a), (b), and (c)	O	-CN	$-CH_3$	-H
E385(a), (b), and (c)	O	-CN	$-CF_3$	-H
E386(a), (b), and (c)	O	-CN	$-OCH_3$	-H
E387(a), (b), and (c)	O	-CN	$-OCH_2CH_3$	-H
E388(a), (b), and (c)	O	-CN	$-OCF_3$	-H
E389(a), (b), and (c)	O	-CN	*-tert*-butyl	-H
E390(a), (b), and (c)	O	-CN	*-iso*-propyl	-H
E391(a), (b), and (c)	O	-CN	$-CH_3$	$-CH_3$
E392(a), (b), and (c)	O	-CN	-H	-H
E393(a), (b), and (c)	O	-CN	-H	-Cl
E394(a), (b), and (c)	O	-CN	-H	-Br
E395(a), (b), and (c)	O	-CN	-H	-F
E396(a), (b), and (c)	O	-CN	-H	$-CH_3$
E397(a), (b), and (c)	O	-CN	-H	$-CF_3$
E398(a), (b), and (c)	O	-CN	-H	$-OCH_3$
E399(a), (b), and (c)	O	-CN	-H	$-OCH_2CH_3$
E400(a), (b), and (c)	O	-CN	-H	$-OCF_3$
E401(a), (b), and (c)	O	-CN	-H	*-tert*-butyl
E402(a), (b), and (c)	O	-CN	-H	*-iso*-propyl
E403(a), (b), and (c)	O	-Br	-Br	-H
E404(a), (b), and (c)	O	-Br	-Cl	-H
E405(a), (b), and (c)	O	-Br	-F	-H
E406(a), (b), and (c)	O	-Br	$-CH_3$	-H
E407(a), (b), and (c)	O	-Br	$-CF_3$	-H
E408(a), (b), and (c)	O	-Br	$-OCH_3$	-H
E409(a), (b), and (c)	O	-Br	$-OCH_2CH_3$	-H

E410(a), (b), and (c)	O	-Br	$-OCF_3$	-H
E411(a), (b), and (c)	O	-Br	-*tert*-butyl	-H
E412(a), (b), and (c)	O	-Br	-*iso*-propyl	-H
E413(a), (b), and (c)	O	-Br	$-CH_3$	$-CH_3$
E414(a), (b), and (c)	O	-Br	-H	-H
E415(a), (b), and (c)	O	-Br	-H	-Cl
E416(a), (b), and (c)	O	-Br	-H	-Br
E417(a), (b), and (c)	O	-Br	-H	-F
E418(a), (b), and (c)	O	-Br	-H	$-CH_3$
E419(a), (b), and (c)	O	-Br	-H	$-CF_3$
E420(a), (b), and (c)	O	-Br	-H	$-OCH_3$
E421(a), (b), and (c)	O	-Br	-H	$-OCH_2CH_3$
E422(a), (b), and (c)	O	-Br	-H	$-OCF_3$
E423(a), (b), and (c)	O	-Br	-H	-*tert*-butyl
E424(a), (b), and (c)	O	-Br	-H	-*iso*-propyl
E425(a), (b), and (c)	O	-I	-Cl	-H
E426(a), (b), and (c)	O	-I	-Br	-H
E427(a), (b), and (c)	O	-I	-F	-H
E428(a), (b), and (c)	O	-I	$-CH_3$	-H
E429(a), (b), and (c)	O	-I	$-CF_3$	-H
E430(a), (b), and (c)	O	-I	$-OCH_3$	-H
E431(a), (b), and (c)	O	-I	$-OCH_2CH_3$	-H
E432(a), (b), and (c)	O	-I	$-OCF_3$	-H
E433(a), (b), and (c)	O	-I	-*tert*-butyl	-H
E434(a), (b), and (c)	O	-I	-*iso*-propyl	-H
E435(a), (b), and (c)	O	-I	$-CH_3$	$-CH_3$
E436(a), (b), and (c)	O	-I	-H	-H
E437(a), (b), and (c)	O	-I	-H	-Cl
E438(a), (b), and (c)	O	-I	-H	-Br
E439(a), (b), and (c)	O	-I	-H	-F
E440(a), (b), and (c)	O	-I	-H	$-CH_3$
E441(a), (b), and (c)	O	-I	-H	$-CF_3$
E442(a), (b), and (c)	O	-I	-H	$-OCH_3$
E443(a), (b), and (c)	O	-I	-H	$-OCH_2CH_3$
E444(a), (b), and (c)	O	-I	-H	$-OCF_3$
E445(a), (b), and (c)	O	-I	-H	-*tert*-butyl
E446(a), (b), and (c)	O	-I	-H	-*iso*-propyl
E447(a), (b), and (c)	NH	-H	-Cl	-H
E448(a), (b), and (c)	NH	-H	-Br	-H
E449(a), (b), and (c)	NH	-H	-F	-H
E450(a), (b), and (c)	NH	-H	$-CH_3$	-H
E451(a), (b), and (c)	NH	-H	$-CF_3$	-H
E452(a), (b), and (c)	NH	-H	$-OCH_3$	-H
E453(a), (b), and (c)	NH	-H	$-OCH_2CH_3$	-H
E454(a), (b), and (c)	NH	-H	$-OCF_3$	-H
E455(a), (b), and (c)	NH	-H	-*tert*-butyl	-H
E456(a), (b), and (c)	NH	-H	-*iso*-propyl	-H
E457(a), (b), and (c)	NH	-H	$-CH_3$	$-CH_3$

E458(a), (b), and (c)	NH	-H	-H	-H
E459(a), (b), and (c)	NH	-H	-H	-Cl
E460(a), (b), and (c)	NH	-H	-H	-Br
E461(a), (b), and (c)	NH	-H	-H	-F
E462(a), (b), and (c)	NH	-H	-H	$-CH_3$
E463(a), (b), and (c)	NH	-H	-H	$-CF_3$
E464(a), (b), and (c)	NH	-H	-H	$-OCH_3$
E465(a), (b), and (c)	NH	-H	-H	$-OCH_2CH_3$
E466(a), (b), and (c)	NH	-H	-H	$-OCF_3$
E467(a), (b), and (c)	NH	-H	-H	*-tert*-butyl
E468(a), (b), and (c)	NH	-H	-H	*-iso*-propyl
E469(a), (b), and (c)	NH	-Cl	-Cl	-H
E470(a), (b), and (c)	NH	-Cl	-Br	-H
E471(a), (b), and (c)	NH	-Cl	-F	-H
E472(a), (b), and (c)	NH	-Cl	$-CH_3$	-H
E473(a), (b), and (c)	NH	-Cl	$-CF_3$	-H
E474(a), (b), and (c)	NH	-Cl	$-OCH_3$	-H
E475(a), (b), and (c)	NH	-Cl	$-OCH_2CH_3$	-H
E476(a), (b), and (c)	NH	-Cl	$-OCF_3$	-H
E477(a), (b), and (c)	NH	-Cl	*-tert*-butyl	-H
E478(a), (b), and (c)	NH	-Cl	*-iso*-propyl	-H
E479(a), (b), and (c)	NH	-Cl	$-CH_3$	$-CH_3$
E480(a), (b), and (c)	NH	-Cl	-H	-H
E481(a), (b), and (c)	NH	-Cl	-H	$-CH_3$
E482(a), (b), and (c)	NH	-Cl	-H	-Cl
E483(a), (b), and (c)	NH	-Cl	-H	-Br
E484(a), (b), and (c)	NH	-Cl	-H	-F
E485(a), (b), and (c)	NH	-Cl	-H	$-CF_3$
E486(a), (b), and (c)	NH	-Cl	-H	$-OCH_3$
E487(a), (b), and (c)	NH	-Cl	-H	$-OCH_2CH_3$
E488(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
E489(a), (b), and (c)	NH	-Cl	-H	*-tert*-butyl
E490(a), (b), and (c)	NH	-Cl	-H	*-iso*-propyl
E491(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
E492(a), (b), and (c)	NH	-Cl	-H	*-tert*-butyl
E493(a), (b), and (c)	NH	-Cl	-H	*-iso*-propyl
E494(a), (b), and (c)	NH	$-CH_3$	-Cl	-H
E495(a), (b), and (c)	NH	$-CH_3$	-Br	-H
E496(a), (b), and (c)	NH	$-CH_3$	-F	-H
E497(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	-H
E498(a), (b), and (c)	NH	$-CH_3$	$-CF_3$	-H
E499(a), (b), and (c)	NH	$-CH_3$	$-OCH_3$	-H
E500(a), (b), and (c)	NH	$-CH_3$	$-OCH_2CH_3$	-H
E501(a), (b), and (c)	NH	$-CH_3$	$-OCF_3$	-H
E502(a), (b), and (c)	NH	$-CH_3$	*-tert*-butyl	-H
E503(a), (b), and (c)	NH	$-CH_3$	*-iso*-propyl	-H
E504(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	$-CH_3$
E505(a), (b), and (c)	NH	$-CH_3$	-H	-H

E506(a), (b), and (c)	NH	$-CH_3$	-H	-Cl
E507(a), (b), and (c)	NH	$-CH_3$	-H	-Br
E508(a), (b), and (c)	NH	$-CH_3$	-H	-F
E509(a), (b), and (c)	NH	$-CH_3$	-H	$-CH_3$
E510(a), (b), and (c)	NH	$-CH_3$	-H	$-CF_3$
E511(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_3$
E512(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_2CH_3$
E513(a), (b), and (c)	NH	$-CH_3$	-H	$-OCF_3$
E514(a), (b), and (c)	NH	$-CH_3$	-H	*-tert*-butyl
E515(a), (b), and (c)	NH	$-CH_3$	-H	*-iso*-propyl
E516(a), (b), and (c)	NH	$-CF_3$	-Cl	-H
E517(a), (b), and (c)	NH	$-CF_3$	-Br	-H
E518(a), (b), and (c)	NH	$-CF_3$	-F	-H
E519(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	-H
E520(a), (b), and (c)	NH	$-CF_3$	$-CF_3$	-H
E521(a), (b), and (c)	NH	$-CF_3$	$-OCH_3$	-H
E522(a), (b), and (c)	NH	$-CF_3$	$-OCH_2CH_3$	-H
E523(a), (b), and (c)	NH	$-CF_3$	$-OCF_3$	-H
E524(a), (b), and (c)	NH	$-CF_3$	*-tert*-butyl	-H
E525(a), (b), and (c)	NH	$-CF_3$	*-iso*-propyl	-H
E526(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	$-CH_3$
E527(a), (b), and (c)	NH	$-CF_3$	-H	-H
E528(a), (b), and (c)	NH	$-CF_3$	-H	-Cl
E529(a), (b), and (c)	NH	$-CF_3$	-H	-Br
E530(a), (b), and (c)	NH	$-CF_3$	-H	-F
E531(a), (b), and (c)	NH	$-CF_3$	-H	$-CH_3$
E532(a), (b), and (c)	NH	$-CF_3$	-H	$-CF_3$
E533(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_3$
E534(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_2CH_3$
E535(a), (b), and (c)	NH	$-CF_3$	-H	$-OCF_3$
E536(a), (b), and (c)	NH	$-CF_3$	-H	*-tert*-butyl
E537(a), (b), and (c)	NH	$-CF_3$	-H	*-iso*-propyl
E538(a), (b), and (c)	NH	$-CHF_2$	-Cl	-H
E539(a), (b), and (c)	NH	$-CHF_2$	-Br	-H
E540(a), (b), and (c)	NH	$-CHF_2$	-F	-H
E541(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	-H
E542(a), (b), and (c)	NH	$-CHF_2$	$-CF_3$	-H
E543(a), (b), and (c)	NH	$-CHF_2$	$-OCH_3$	-H
E544(a), (b), and (c)	NH	$-CHF_2$	$-OCH_2CH_3$	-H
E545(a), (b), and (c)	NH	$-CHF_2$	$-OCF_3$	-H
E546(a), (b), and (c)	NH	$-CHF_2$	*-tert*-butyl	-H
E547(a), (b), and (c)	NH	$-CHF_2$	*-iso*-propyl	-H
E548(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	$-CH_3$
E549(a), (b), and (c)	NH	$-CHF_2$	-H	-H
E550(a), (b), and (c)	NH	$-CHF_2$	-H	-Cl
E551(a), (b), and (c)	NH	$-CHF_2$	-H	-Br
E552(a), (b), and (c)	NH	$-CHF_2$	-H	-F
E553(a), (b), and (c)	NH	$-CHF_2$	-H	$-CH_3$

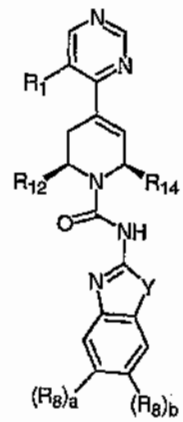
E554(a), (b), and (c)	NH	$-CHF_2$	-H	$-CF_3$
E555(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_3$
E556(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_2CH_3$
E557(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCF_3$
E558(a), (b), and (c)	NH	$-CHF_2$	-H	*-tert*-butyl
E559(a), (b), and (c)	NH	$-CHF_2$	-H	*-iso*-propyl
E560(a), (b), and (c)	NH	-OH	-Cl	-H
E561(a), (b), and (c)	NH	-OH	-Br	-H
E562(a), (b), and (c)	NH	-OH	-F	-H
E563(a), (b), and (c)	NH	-OH	$-CH_3$	-H
E564(a), (b), and (c)	NH	-OH	$-CF_3$	-H
E565(a), (b), and (c)	NH	-OH	$-OCH_3$	-H
E566(a), (b), and (c)	NH	-OH	$-OCH_2CH_3$	-H
E567(a), (b), and (c)	NH	-OH	$-OCF_3$	-H
E568(a), (b), and (c)	NH	-OH	*-tert*-butyl	-H
E569(a), (b), and (c)	NH	-OH	*-iso*-propyl	-H
E570(a), (b), and (c)	NH	-OH	$-CH_3$	$-CH_3$
E571(a), (b), and (c)	NH	-OH	-H	-H
E572(a), (b), and (c)	NH	-OH	-H	-Cl
E573(a), (b), and (c)	NH	-OH	-H	-Br
E574(a), (b), and (c)	NH	-OH	-H	-F
E575(a), (b), and (c)	NH	-OH	-H	$-CH_3$
E576(a), (b), and (c)	NH	-OH	-H	$-CF_3$
E577(a), (b), and (c)	NH	-OH	-H	$-OCH_3$
E578(a), (b), and (c)	NH	-OH	-H	$-OCH_2CH_3$
E579(a), (b), and (c)	NH	-OH	-H	$-OCF_3$
E580(a), (b), and (c)	NH	-OH	-H	*-tert*-butyl
E581(a), (b), and (c)	NH	-OH	-H	*-iso*-propyl
E582(a), (b), and (c)	NH	$-NO_2$	-Cl	-H
E583(a), (b), and (c)	NH	$-NO_2$	-Br	-H
E584(a), (b), and (c)	NH	$-NO_2$	-F	-H
E585(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	-H
E586(a), (b), and (c)	NH	$-NO_2$	$-CF_3$	-H
E587(a), (b), and (c)	NH	$-NO_2$	$-OCH_3$	-H
E588(a), (b), and (c)	NH	$-NO_2$	$-OCH_2CH_3$	-H
E589(a), (b), and (c)	NH	$-NO_2$	$-OCF_3$	-H
E590(a), (b), and (c)	NH	$-NO_2$	*-tert*-butyl	-H
E591(a), (b), and (c)	NH	$-NO_2$	*-iso*-propyl	-H
E592(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	$-CH_3$
E593(a), (b), and (c)	NH	$-NO_2$	-H	-H
E594(a), (b), and (c)	NH	$-NO_2$	-H	-Cl
E595(a), (b), and (c)	NH	$-NO_2$	-H	-Br
E596(a), (b), and (c)	NH	$-NO_2$	-H	-F
E597(a), (b), and (c)	NH	$-NO_2$	-H	$-CH_3$
E598(a), (b), and (c)	NH	$-NO_2$	-H	$-CF_3$
E599(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_3$
E600(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_2CH_3$
E601(a), (b), and (c)	NH	$-NO_2$	-H	$-OCF_3$

E602(a), (b), and (c)	NH	$-NO_2$	-H	-*tert*-butyl
E603(a), (b), and (c)	NH	$-NO_2$	-H	-*iso*-propyl
E604(a), (b), and (c)	NH	-CN	-Br	-H
E605(a), (b), and (c)	NH	-CN	-Cl	-H
E606(a), (b), and (c)	NH	-CN	-F	-H
E607(a), (b), and (c)	NH	-CN	$-CH_3$	-H
E608(a), (b), and (c)	NH	-CN	$-CF_3$	-H
E609(a), (b), and (c)	NH	-CN	$-OCH_3$	-H
E610(a), (b), and (c)	NH	-CN	$-OCH_2CH_3$	-H
E611(a), (b), and (c)	NH	-CN	$-OCF_3$	-H
E612(a), (b), and (c)	NH	-CN	-*tert*-butyl	-H
E613(a), (b), and (c)	NH	-CN	-*iso*-propyl	-H
E614(a), (b), and (c)	NH	-CN	$-CH_3$	$-CH_3$
E615(a), (b), and (c)	NH	-CN	-H	-H
E616(a), (b), and (c)	NH	-CN	-H	-Cl
E617(a), (b), and (c)	NH	-CN	-H	-Br
E618(a), (b), and (c)	NH	-CN	-H	-F
E619(a), (b), and (c)	NH	-CN	-H	$-CH_3$
E620(a), (b), and (c)	NH	-CN	-H	$-CF_3$
E621(a), (b), and (c)	NH	-CN	-H	$-OCH_3$
E622(a), (b), and (c)	NH	-CN	-H	$-OCH_2CH_3$
E623(a), (b), and (c)	NH	-CN	-H	$-OCF_3$
E624(a), (b), and (c)	NH	-CN	-H	-*tert*-butyl
E625(a), (b), and (c)	NH	-CN	-H	-*iso*-propyl
E626(a), (b), and (c)	NH	-Br	-Br	-H
E627(a), (b), and (c)	NH	-Br	-Cl	-H
E628(a), (b), and (c)	NH	-Br	-F	-H
E629(a), (b), and (c)	NH	-Br	$-CH_3$	-H
E630(a), (b), and (c)	NH	-Br	$-CF_3$	-H
E631(a), (b), and (c)	NH	-Br	$-OCH_3$	-H
E632(a), (b), and (c)	NH	-Br	$-OCH_2CH_3$	-H
E633(a), (b), and (c)	NH	-Br	$-OCF_3$	-H
E634(a), (b), and (c)	NH	-Br	-*tert*-butyl	-H
E635(a), (b), and (c)	NH	-Br	-*iso*-propyl	-H
E636(a), (b), and (c)	NH	-Br	$-CH_3$	$-CH_3$
E637(a), (b), and (c)	NH	-Br	-H	-H
E638(a), (b), and (c)	NH	-Br	-H	-Cl
E639(a), (b), and (c)	NH	-Br	-H	-Br
E640(a), (b), and (c)	NH	-Br	-H	-F
E641(a), (b), and (c)	NH	-Br	-H	$-CH_3$
E642(a), (b), and (c)	NH	-Br	-H	$-CF_3$
E643(a), (b), and (c)	NH	-Br	-H	$-OCH_3$
E644(a), (b), and (c)	NH	-Br	-H	$-OCH_2CH_3$
E645(a), (b), and (c)	NH	-Br	-H	$-OCF_3$
E646(a), (b), and (c)	NH	-Br	-H	-*tert*-butyl
E647(a), (b), and (c)	NH	-Br	-H	-*iso*-propyl
E648(a), (b), and (c)	NH	-I	-Cl	-H
E649(a), (b), and (c)	NH	-I	-Br	-H

E650(a), (b), and (c)	NH	-I	-F	-H
E651(a), (b), and (c)	NH	-I	$-CH_3$	-H
E652(a), (b), and (c)	NH	-I	$-CF_3$	-H
E653(a), (b), and (c)	NH	-I	$-OCH_3$	-H
E654(a), (b), and (c)	NH	-I	$-OCH_2CH_3$	-H
E655(a), (b), and (c)	NH	-I	$-OCF_3$	-H
E656(a), (b), and (c)	NH	-I	-*tert*-butyl	-H
E657(a), (b), and (c)	NH	-I	-*iso*-propyl	-H
E658(a), (b), and (c)	NH	-I	$-CH_3$	$-CH_3$
E659(a), (b), and (c)	NH	-I	-H	-H
E660(a), (b), and (c)	NH	-I	-H	-Cl
E661(a), (b), and (c)	NH	-I	-H	-Br
E662(a), (b), and (c)	NH	-I	-H	-F
E663(a), (b), and (c)	NH	-I	-H	$-CH_3$
E664(a), (b), and (c)	NH	-I	-H	$-CF_3$
E665(a), (b), and (c)	NH	-I	-H	$-OCH_3$
E666(a), (b), and (c)	NH	-I	-H	$-OCH_2CH_3$
E667(a), (b), and (c)	NH	-I	-H	$-OCF_3$
E668(a), (b), and (c)	NH	-I	-H	-*tert*-butyl
E669(a), (b), and (c)	NH	-I	-H	-*iso*-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 6



(If)

and pharmaceutically acceptable salts thereof, where:

Compound	Y	R_1	$(R_8)_a$	$(R_8)_b$
F01(a), (b), and (c)	S	-H	-Cl	-H
F02(a), (b), and (c)	S	-H	-Br	-H
F03(a), (b), and (c)	S	-H	-F	-H
F04(a), (b), and (c)	S	-H	$-CH_3$	-H
F05(a), (b), and (c)	S	-H	$-CF_3$	-H
F06(a), (b), and (c)	S	-H	$-OCH_3$	-H
F07(a), (b), and (c)	S	-H	$-OCH_2CH_3$	-H
F08(a), (b), and (c)	S	-H	$-OCF_3$	-H
F09(a), (b), and (c)	S	-H	-*tert*-butyl	-H
F10(a), (b), and (c)	S	-H	-*iso*-propyl	-H
F11(a), (b), and (c)	S	-H	$-CH_3$	$-CH_3$
F12(a), (b), and (c)	S	-H	-H	-H
F13(a), (b), and (c)	S	-H	-H	-Cl
F14(a), (b), and (c)	S	-H	-H	-Br
F15(a), (b), and (c)	S	-H	-H	-F
F16(a), (b), and (c)	S	-H	-H	$-CH_3$
F17(a), (b), and (c)	S	-H	-H	$-CF_3$
F18(a), (b), and (c)	S	-H	-H	$-OCH_3$
F19(a), (b), and (c)	S	-H	-H	$-OCH_2CH_3$
F20(a), (b), and (c)	S	-H	-H	$-OCF_3$
F21(a), (b), and (c)	S	-H	-H	-*tert*-butyl
F22(a), (b), and (c)	S	-H	-H	-*iso*-propyl
F23(a), (b), and (c)	S	-Cl	-Cl	-H
F24(a), (b), and (c)	S	-Cl	-Br	-H
F25(a), (b), and (c)	S	-Cl	-F	-H
F26(a), (b), and (c)	S	-Cl	$-CH_3$	-H
F27(a), (b), and (c)	S	-Cl	$-CF_3$	-H

F28(a), (b), and (c)	S	-Cl	$-OCH_3$	-H
F29(a), (b), and (c)	S	-Cl	$-OCH_2CH_3$	-H
F30(a), (b), and (c)	S	-Cl	$-OCF_3$	-H
F31(a), (b), and (c)	S	-Cl	-*tert*-butyl	-H
F32(a), (b), and (c)	S	-Cl	-*iso*-propyl	-H
F33(a), (b), and (c)	S	-Cl	$-CH_3$	$-CH_3$
F34(a), (b), and (c)	S	-Cl	-H	-H
F35(a), (b), and (c)	S	-Cl	-H	-Cl
F36(a), (b), and (c)	S	-Cl	-H	-Br
F37(a), (b), and (c)	S	-Cl	-H	-F
F38(a), (b), and (c)	S	-Cl	-H	$-CH_3$
F39(a), (b), and (c)	S	-Cl	-H	$-CF_3$
F40(a), (b), and (c)	S	-Cl	-H	$-OCH_3$
F41(a), (b), and (c)	S	-Cl	-H	$-OCH_2CH_3$
F42(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
F43(a), (b), and (c)	S	-Cl	-H	-*tert*-butyl
F44(a), (b), and (c)	S	-Cl	-H	-*iso*-propyl
F45(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
F46(a), (b), and (c)	S	-Cl	-H	-*tert*-butyl
F47(a), (b), and (c)	S	-Cl	-H	-*iso*-propyl
F48(a), (b), and (c)	S	$-CH_3$	-Cl	-H
F49(a), (b), and (c)	S	$-CH_3$	-Br	-H
F50(a), (b), and (c)	S	$-CH_3$	-F	-H
F51(a), (b), and (c)	S	$-CH_3$	$-CH_3$	-H
F52(a), (b), and (c)	S	$-CH_3$	$-CF_3$	-H
F53(a), (b), and (c)	S	$-CH_3$	$-OCH_3$	-H
F54(a), (b), and (c)	S	$-CH_3$	$-OCH_2CH_3$	-H
F55(a), (b), and (c)	S	$-CH_3$	$-OCF_3$	-H
F56(a), (b), and (c)	S	$-CH_3$	-*tert*-butyl	-H
F57(a), (b), and (c)	S	$-CH_3$	-*iso*-propyl	-H
F58(a), (b), and (c)	S	$-CH_3$	$-CH_3$	$-CH_3$
F59(a), (b), and (c)	S	$-CH_3$	-H	-H
F60(a), (b), and (c)	S	$-CH_3$	-H	-Cl
F61(a), (b), and (c)	S	$-CH_3$	-H	-Br
F62(a), (b), and (c)	S	$-CH_3$	-H	-F
F63(a), (b), and (c)	S	$-CH_3$	-H	$-CH_3$
F64(a), (b), and (c)	S	$-CH_3$	-H	$-CF_3$
F65(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_3$
F66(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_2CH_3$
F67(a), (b), and (c)	S	$-CH_3$	-H	$-OCF_3$
F68(a), (b), and (c)	S	$-CH_3$	-H	-*tert*-butyl
F69(a), (b), and (c)	S	$-CH_3$	-H	-*iso*-propyl
F70(a), (b), and (c)	S	$-CF_3$	-Cl	-H
F71(a), (b), and (c)	S	$-CF_3$	-Br	-H
F72(a), (b), and (c)	S	$-CF_3$	-F	-H
F73(a), (b), and (c)	S	$-CF_3$	$-CH_3$	-H
F74(a), (b), and (c)	S	$-CF_3$	$-CF_3$	-H
F75(a), (b), and (c)	S	$-CF_3$	$-OCH_3$	-H

F76(a), (b), and (c)	S	$-CF_3$	$-OCH_2CH_3$	-H
F77(a), (b), and (c)	S	$-CF_3$	$-OCF_3$	-H
F78(a), (b), and (c)	S	$-CF_3$	*-tert*-butyl	-H
F79(a), (b), and (c)	S	$-CF_3$	*-iso*-propyl	-H
F80(a), (b), and (c)	S	$-CF_3$	$-CH_3$	$-CH_3$
F81(a), (b), and (c)	S	$-CF_3$	-H	-H
F82(a), (b), and (c)	S	$-CF_3$	-H	-Cl
F83(a), (b), and (c)	S	$-CF_3$	-H	-Br
F84(a), (b), and (c)	S	$-CF_3$	-H	-F
F85(a), (b), and (c)	S	$-CF_3$	-H	$-CH_3$
F86(a), (b), and (c)	S	$-CF_3$	-H	$-CF_3$
F87(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_3$
F88(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_2CH_3$
F89(a), (b), and (c)	S	$-CF_3$	-H	$-OCF_3$
F90(a), (b), and (c)	S	$-CF_3$	-H	*-tert*-butyl
F91(a), (b), and (c)	S	$-CF_3$	-H	*-iso*-propyl
F92(a), (b), and (c)	S	$-CHF_2$	-Cl	-H
F93(a), (b), and (c)	S	$-CHF_2$	-Br	-H
F94(a), (b), and (c)	S	$-CHF_2$	-F	-H
F95(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	-H
F96(a), (b), and (c)	S	$-CHF_2$	$-CF_3$	-H
F97(a), (b), and (c)	S	$-CHF_2$	$-OCH_3$	-H
F98(a), (b), and (c)	S	$-CHF_2$	$-OCH_2CH_3$	-H
F99(a), (b), and (c)	S	$-CHF_2$	$-OCF_3$	-H
F100(a), (b), and (c)	S	$-CHF_2$	*-tert*-butyl	-H
F101(a), (b), and (c)	S	$-CHF_2$	*-iso*-propyl	-H
F102(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	$-CH_3$
F103(a), (b), and (c)	S	$-CHF_2$	-H	-H
F104(a), (b), and (c)	S	$-CHF_2$	-H	-Cl
F105(a), (b), and (c)	S	$-CHF_2$	-H	-Br
F106(a), (b), and (c)	S	$-CHF_2$	-H	-F
F107(a), (b), and (c)	S	$-CHF_2$	-H	$-CH_3$
F108(a), (b), and (c)	S	$-CHF_2$	-H	$-CF_3$
F109(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_3$
F110(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_2CH_3$
F111(a), (b), and (c)	S	$-CHF_2$	-H	$-OCF_3$
F112(a), (b), and (c)	S	$-CHF_2$	-H	*-tert*-butyl
F113(a), (b), and (c)	S	$-CHF_2$	-H	*-iso*-propyl
F114(a), (b), and (c)	S	-OH	-Cl	-H
F115(a), (b), and (c)	S	-OH	-Br	-H
F116(a), (b), and (c)	S	-OH	-F	-H
F117(a), (b), and (c)	S	-OH	$-CH_3$	-H
F118(a), (b), and (c)	S	-OH	$-CF_3$	-H
F119(a), (b), and (c)	S	-OH	$-OCH_3$	-H
F120(a), (b), and (c)	S	-OH	$-OCH_2CH_3$	-H
F121(a), (b), and (c)	S	-OH	$-OCF_3$	-H
F122(a), (b), and (c)	S	-OH	*-tert*-butyl	-H
F123(a), (b), and (c)	S	-OH	*-iso*-propyl	-H

F124(a), (b), and (c)	S	-OH	$-CH_3$	$-CH_3$
F125(a), (b), and (c)	S	-OH	-H	-H
F126(a), (b), and (c)	S	-OH	-H	-Cl
F127(a), (b), and (c)	S	-OH	-H	-Br
F128(a), (b), and (c)	S	-OH	-H	-F
F129(a), (b), and (c)	S	-OH	-H	$-CH_3$
F130(a), (b), and (c)	S	-OH	-H	$-CF_3$
F131(a), (b), and (c)	S	-OH	-H	$-OCH_3$
F132(a), (b), and (c)	S	-OH	-H	$-OCH_2CH_3$
F133(a), (b), and (c)	S	-OH	-H	$-OCF_3$
F134(a), (b), and (c)	S	-OH	-H	-*tert*-butyl
F135(a), (b), and (c)	S	-OH	-H	-*iso*-propyl
F136(a), (b), and (c)	S	$-NO_2$	-Cl	-H
F137(a), (b), and (c)	S	$-NO_2$	-Br	-H
F138(a), (b), and (c)	S	$-NO_2$	-F	-H
F139(a), (b), and (c)	S	$-NO_2$	$-CH_3$	-H
F140(a), (b), and (c)	S	$-NO_2$	$-CF_3$	-H
F141(a), (b), and (c)	S	$-NO_2$	$-OCH_3$	-H
F142(a), (b), and (c)	S	$-NO_2$	$-OCH_2CH_3$	-H
F143(a), (b), and (c)	S	$-NO_2$	$-OCF_3$	-H
F144(a), (b), and (c)	S	$-NO_2$	-*tert*-butyl	-H
F145(a), (b), and (c)	S	$-NO_2$	-*iso*-propyl	-H
F146(a), (b), and (c)	S	$-NO_2$	$-CH_3$	$-CH_3$
F147(a), (b), and (c)	S	$-NO_2$	-H	-H
F148(a), (b), and (c)	S	$-NO_2$	-H	-Cl
F149(a), (b), and (c)	S	$-NO_2$	-H	-Br
F150(a), (b), and (c)	S	$-NO_2$	-H	-F
F151(a), (b), and (c)	S	$-NO_2$	-H	$-CH_3$
F152(a), (b), and (c)	S	$-NO_2$	-H	$-CF_3$
F153(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_3$
F154(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_2CH_3$
F155(a), (b), and (c)	S	$-NO_2$	-H	$-OCF_3$
F156(a), (b), and (c)	S	$-NO_2$	-H	-*tert*-butyl
F157(a), (b), and (c)	S	$-NO_2$	-H	-*iso*-propyl
F158(a), (b), and (c)	S	-CN	-Br	-H
F159(a), (b), and (c)	S	-CN	-Cl	-H
F160(a), (b), and (c)	S	-CN	-F	-H
F161(a), (b), and (c)	S	-CN	$-CH_3$	-H
F162(a), (b), and (c)	S	-CN	$-CF_3$	-H
F163(a), (b), and (c)	S	-CN	$-OCH_3$	-H
F164(a), (b), and (c)	S	-CN	$-OCH_2CH_3$	-H
F165(a), (b), and (c)	S	-CN	$-OCF_3$	-H
F166(a), (b), and (c)	S	-CN	-*tert*-butyl	-H
F167(a), (b), and (c)	S	-CN	-*iso*-propyl	-H
F168(a), (b), and (c)	S	-CN	$-CH_3$	$-CH_3$
F169(a), (b), and (c)	S	-CN	-H	-H
F170(a), (b), and (c)	S	-CN	-H	-Cl
F171(a), (b), and (c)	S	-CN	-H	-Br

F172(a), (b), and (c)	S	-CN	-H	-F
F173(a), (b), and (c)	S	-CN	-H	$-CH_3$
F174(a), (b), and (c)	S	-CN	-H	$-CF_3$
F175(a), (b), and (c)	S	-CN	-H	$-OCH_3$
F176(a), (b), and (c)	S	-CN	-H	$-OCH_2CH_3$
F177(a), (b), and (c)	S	-CN	-H	$-OCF_3$
F178(a), (b), and (c)	S	-CN	-H	*-tert*-butyl
F179(a), (b), and (c)	S	-CN	-H	*-iso*-propyl
F180(a), (b), and (c)	S	-Br	-Br	-H
F181(a), (b), and (c)	S	-Br	-Cl	-H
F182(a), (b), and (c)	S	-Br	-F	-H
F183(a), (b), and (c)	S	-Br	$-CH_3$	-H
F184(a), (b), and (c)	S	-Br	$-CF_3$	-H
F185(a), (b), and (c)	S	-Br	$-OCH_3$	-H
F186(a), (b), and (c)	S	-Br	$-OCH_2CH_3$	-H
F187(a), (b), and (c)	S	-Br	$-OCF_3$	-H
F188(a), (b), and (c)	S	-Br	*-tert*-butyl	-H
F189(a), (b), and (c)	S	-Br	*-iso*-propyl	-H
F190(a), (b), and (c)	S	-Br	$-CH_3$	$-CH_3$
F191(a), (b), and (c)	S	-Br	-H	-H
F192(a), (b), and (c)	S	-Br	-H	-Cl
F193(a), (b), and (c)	S	-Br	-H	-Br
F194(a), (b), and (c)	S	-Br	-H	-F
F195(a), (b), and (c)	S	-Br	-H	$-CH_3$
F196(a), (b), and (c)	S	-Br	-H	$-CF_3$
F197(a), (b), and (c)	S	-Br	-H	$-OCH_3$
F198(a), (b), and (c)	S	-Br	-H	$-OCH_2CH_3$
F199(a), (b), and (c)	S	-Br	-H	$-OCF_3$
F200(a), (b), and (c)	S	-Br	-H	*-tert*-butyl
F201(a), (b), and (c)	S	-Br	-H	*-iso*-propyl
F202(a), (b), and (c)	S	-I	-Cl	-H
F203(a), (b), and (c)	S	-I	-Br	-H
F204(a), (b), and (c)	S	-I	-F	-H
F205(a), (b), and (c)	S	-I	$-CH_3$	-H
F206(a), (b), and (c)	S	-I	$-CF_3$	-H
F207(a), (b), and (c)	S	-I	$-OCH_3$	-H
F208(a), (b), and (c)	S	-I	$-OCH_2CH_3$	-H
F209(a), (b), and (c)	S	-I	$-OCF_3$	-H
F210(a), (b), and (c)	S	-I	*-tert*-butyl	-H
F211(a), (b), and (c)	S	-I	*-iso*-propyl	-H
F212(a), (b), and (c)	S	-I	$-CH_3$	$-CH_3$
F213(a), (b), and (c)	S	-I	-H	-H
F214(a), (b), and (c)	S	-I	-H	-Cl
F215(a), (b), and (c)	S	-I	-H	-Br
F216(a), (b), and (c)	S	-I	-H	-F
F217(a), (b), and (c)	S	-I	-H	$-CH_3$
F218(a), (b), and (c)	S	-I	-H	$-CF_3$
F219(a), (b), and (c)	S	-I	-H	$-OCH_3$

F220(a), (b), and (c)	S	-I	-H	$-OCH_2CH_3$
F221(a), (b), and (c)	S	-I	-H	$-OCF_3$
F222(a), (b), and (c)	S	-I	-H	*-tert*-butyl
F223(a), (b), and (c)	S	-I	-H	*-iso*-propyl
F224(a), (b), and (c)	O	-H	-Cl	-H
F225(a), (b), and (c)	O	-H	-Br	-H
F226(a), (b), and (c)	O	-H	-F	-H
F227(a), (b), and (c)	O	-H	$-CH_3$	-H
F228(a), (b), and (c)	O	-H	$-CF_3$	-H
F229(a), (b), and (c)	O	-H	$-OCH_3$	-H
F230(a), (b), and (c)	O	-H	$-OCH_2CH_3$	-H
F231(a), (b), and (c)	O	-H	$-OCF_3$	-H
F232(a), (b), and (c)	O	-H	*-tert*-butyl	-H
F233(a), (b), and (c)	O	-H	*-iso*-propyl	-H
F234(a), (b), and (c)	O	-H	$-CH_3$	$-CH_3$
F235(a), (b), and (c)	O	-H	-H	-H
F236(a), (b), and (c)	O	-H	-H	-Cl
F237(a), (b), and (c)	O	-H	-H	-Br
F238(a), (b), and (c)	O	-H	-H	-F
F239(a), (b), and (c)	O	-H	-H	$-CH_3$
F240(a), (b), and (c)	O	-H	-H	$-CF_3$
F241(a), (b), and (c)	O	-H	-H	$-OCH_3$
F242(a), (b), and (c)	O	-H	-H	$-OCH_2CH_3$
F243(a), (b), and (c)	O	-H	-H	$-OCF_3$
F244(a), (b), and (c)	O	-H	-H	*-tert*-butyl
F245(a), (b), and (c)	O	-H	-H	*-iso*-propyl
F246(a), (b), and (c)	O	-Cl	-Cl	-H
F247(a), (b), and (c)	O	-Cl	-Br	-H
F248(a), (b), and (c)	O	-Cl	-F	-H
F249(a), (b), and (c)	O	-Cl	$-CH_3$	-H
F250(a), (b), and (c)	O	-Cl	$-CF_3$	-H
F251(a), (b), and (c)	O	-Cl	$-OCH_3$	-H
F252(a), (b), and (c)	O	-Cl	$-OCH_2CH_3$	-H
F253(a), (b), and (c)	O	-Cl	$-OCF_3$	-H
F254(a), (b), and (c)	O	-Cl	*-tert*-butyl	-H
F255(a), (b), and (c)	O	-Cl	*-iso*-propyl	-H
F256(a), (b), and (c)	O	-Cl	$-CH_3$	$-CH_3$
F257(a), (b), and (c)	O	-Cl	-H	-H
F258(a), (b), and (c)	O	-Cl	-H	$-CH_3$
F259(a), (b), and (c)	O	-Cl	-H	-Cl
F260(a), (b), and (c)	O	-Cl	-H	-Br
F261(a), (b), and (c)	O	-Cl	-H	-F
F262(a), (b), and (c)	O	-Cl	-H	$-CF_3$
F263(a), (b), and (c)	O	-Cl	-H	$-OCH_3$
F264(a), (b), and (c)	O	-Cl	-H	$-OCH_2CH_3$
F265(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
F266(a), (b), and (c)	O	-Cl	-H	*-tert*-butyl
F267(a), (b), and (c)	O	-Cl	-H	*-iso*-propyl

F268(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
F269(a), (b), and (c)	O	-Cl	-H	-*tert*-butyl
F270(a), (b), and (c)	O	-Cl	-H	-*iso*-propyl
F271(a), (b), and (c)	O	$-CH_3$	-Cl	-H
F272(a), (b), and (c)	O	$-CH_3$	-Br	-H
F273(a), (b), and (c)	O	$-CH_3$	-F	-H
F274(a), (b), and (c)	O	$-CH_3$	$-CH_3$	-H
F275(a), (b), and (c)	O	$-CH_3$	$-CF_3$	-H
F276(a), (b), and (c)	O	$-CH_3$	$-OCH_3$	-H
F277(a), (b), and (c)	O	$-CH_3$	$-OCH_2CH_3$	-H
F278(a), (b), and (c)	O	$-CH_3$	$-OCF_3$	-H
F279(a), (b), and (c)	O	$-CH_3$	-*tert*-butyl	-H
F280(a), (b), and (c)	O	$-CH_3$	-*iso*-propyl	-H
F281(a), (b), and (c)	O	$-CH_3$	$-CH_3$	$-CH_3$
F282(a), (b), and (c)	O	$-CH_3$	-H	-H
F283(a), (b), and (c)	O	$-CH_3$	-H	-Cl
F284(a), (b), and (c)	O	$-CH_3$	-H	-Br
F285(a), (b), and (c)	O	$-CH_3$	-H	-F
F286(a), (b), and (c)	O	$-CH_3$	-H	$-CH_3$
F287(a), (b), and (c)	O	$-CH_3$	-H	$-CF_3$
F288(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_3$
F289(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_2CH_3$
F290(a), (b), and (c)	O	$-CH_3$	-H	$-OCF_3$
F291(a), (b), and (c)	O	$-CH_3$	-H	-*tert*-butyl
F292(a), (b), and (c)	O	$-CH_3$	-H	-*iso*-propyl
F293(a), (b), and (c)	O	$-CF_3$	-Cl	-H
F294(a), (b), and (c)	O	$-CF_3$	-Br	-H
F295(a), (b), and (c)	O	$-CF_3$	-F	-H
F296(a), (b), and (c)	O	$-CF_3$	$-CH_3$	-H
F297(a), (b), and (c)	O	$-CF_3$	$-CF_3$	-H
F298(a), (b), and (c)	O	$-CF_3$	$-OCH_3$	-H
F299(a), (b), and (c)	O	$-CF_3$	$-OCH_2CH_3$	-H
F300(a), (b), and (c)	O	$-CF_3$	$-OCF_3$	-H
F301(a), (b), and (c)	O	$-CF_3$	-*tert*-butyl	-H
F302(a), (b), and (c)	O	$-CF_3$	-*iso*-propyl	-H
F303(a), (b), and (c)	O	$-CF_3$	$-CH_3$	$-CH_3$
F304(a), (b), and (c)	O	$-CF_3$	-H	-H
F305(a), (b), and (c)	O	$-CF_3$	-H	-Cl
F306(a), (b), and (c)	O	$-CF_3$	-H	-Br
F307(a), (b), and (c)	O	$-CF_3$	-H	-F
F308(a), (b), and (c)	O	$-CF_3$	-H	$-CH_3$
F309(a), (b), and (c)	O	$-CF_3$	-H	$-CF_3$
F310(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_3$
F311(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_2CH_3$
F312(a), (b), and (c)	O	$-CF_3$	-H	$-OCF_3$
F313(a), (b), and (c)	O	$-CF_3$	-H	-*tert*-butyl
F314(a), (b), and (c)	O	$-CF_3$	-H	-*iso*-propyl
F315(a), (b), and (c)	O	$-CHF_2$	-Cl	-H

F316(a), (b), and (c)	O	$-CHF_2$	-Br	-H
F317(a), (b), and (c)	O	$-CHF_2$	-F	-H
F318(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	-H
F319(a), (b), and (c)	O	$-CHF_2$	$-CF_3$	-H
F320(a), (b), and (c)	O	$-CHF_2$	$-OCH_3$	-H
F321(a), (b), and (c)	O	$-CHF_2$	$-OCH_2CH_3$	-H
F322(a), (b), and (c)	O	$-CHF_2$	$-OCF_3$	-H
F323(a), (b), and (c)	O	$-CHF_2$	-*tert*-butyl	-H
F324(a), (b), and (c)	O	$-CHF_2$	-*iso*-propyl	-H
F325(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	$-CH_3$
F326(a), (b), and (c)	O	$-CHF_2$	-H	-H
F327(a), (b), and (c)	O	$-CHF_2$	-H	-Cl
F328(a), (b), and (c)	O	$-CHF_2$	-H	-Br
F329(a), (b), and (c)	O	$-CHF_2$	-H	-F
F330(a), (b), and (c)	O	$-CHF_2$	-H	$-CH_3$
F331(a), (b), and (c)	O	$-CHF_2$	-H	$-CF_3$
F332(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_3$
F333(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_2CH_3$
F334(a), (b), and (c)	O	$-CHF_2$	-H	$-OCF_3$
F335(a), (b), and (c)	O	$-CHF_2$	-H	-*tert*-butyl
F336(a), (b), and (c)	O	$-CHF_2$	-H	-*iso*-propyl
F337(a), (b), and (c)	O	-OH	-Cl	-H
F338(a), (b), and (c)	O	-OH	-Br	-H
F339(a), (b), and (c)	O	-OH	-F	-H
F340(a), (b), and (c)	O	-OH	$-CH_3$	-H
F341(a), (b), and (c)	O	-OH	$-CF_3$	-H
F342(a), (b), and (c)	O	-OH	$-OCH_3$	-H
F343(a), (b), and (c)	O	-OH	$-OCH_2CH_3$	-H
F344(a), (b), and (c)	O	-OH	$-OCF_3$	-H
F345(a), (b), and (c)	O	-OH	-*tert*-butyl	-H
F346(a), (b), and (c)	O	-OH	-*iso*-propyl	-H
F347(a), (b), and (c)	O	-OH	$-CH_3$	$-CH_3$
F348(a), (b), and (c)	O	-OH	-H	-H
F349(a), (b), and (c)	O	-OH	-H	-Cl
F350(a), (b), and (c)	O	-OH	-H	-Br
F351(a), (b), and (c)	O	-OH	-H	-F
F352(a), (b), and (c)	O	-OH	-H	$-CH_3$
F353(a), (b), and (c)	O	-OH	-H	$-CF_3$
F354(a), (b), and (c)	O	-OH	-H	$-OCH_3$
F355(a), (b), and (c)	O	-OH	-H	$-OCH_2CH_3$
F356(a), (b), and (c)	O	-OH	-H	$-OCF_3$
F357(a), (b), and (c)	O	-OH	-H	-*tert*-butyl
F358(a), (b), and (c)	O	-OH	-H	-*iso*-propyl
F359(a), (b), and (c)	O	$-NO_2$	-Cl	-H
F360(a), (b), and (c)	O	$-NO_2$	-Br	-H
F361(a), (b), and (c)	O	$-NO_2$	-F	-H
F362(a), (b), and (c)	O	$-NO_2$	$-CH_3$	-H
F363(a), (b), and (c)	O	$-NO_2$	$-CF_3$	-H

F364(a), (b), and (c)	O	$-NO_2$	$-OCH_3$	-H
F365(a), (b), and (c)	O	$-NO_2$	$-OCH_2CH_3$	-H
F366(a), (b), and (c)	O	$-NO_2$	$-OCF_3$	-H
F367(a), (b), and (c)	O	$-NO_2$	-*tert*-butyl	-H
F368(a), (b), and (c)	O	$-NO_2$	-*iso*-propyl	-H
F369(a), (b), and (c)	O	$-NO_2$	$-CH_3$	$-CH_3$
F370(a), (b), and (c)	O	$-NO_2$	-H	-H
F371(a), (b), and (c)	O	$-NO_2$	-H	-Cl
F372(a), (b), and (c)	O	$-NO_2$	-H	-Br
F373(a), (b), and (c)	O	$-NO_2$	-H	-F
F374(a), (b), and (c)	O	$-NO_2$	-H	$-CH_3$
F375(a), (b), and (c)	O	$-NO_2$	-H	$-CF_3$
F376(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_3$
F377(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_2CH_3$
F378(a), (b), and (c)	O	$-NO_2$	-H	$-OCF_3$
F379(a), (b), and (c)	O	$-NO_2$	-H	-*tert*-butyl
F380(a), (b), and (c)	O	$-NO_2$	-H	-*iso*-propyl
F381(a), (b), and (c)	O	-CN	-Br	-H
F382(a), (b), and (c)	O	-CN	-Cl	-H
F383(a), (b), and (c)	O	-CN	-F	-H
F384(a), (b), and (c)	O	-CN	$-CH_3$	-H
F385(a), (b), and (c)	O	-CN	$-CF_3$	-H
F386(a), (b), and (c)	O	-CN	$-OCH_3$	-H
F387(a), (b), and (c)	O	-CN	$-OCH_2CH_3$	-H
F388(a), (b), and (c)	O	-CN	$-OCF_3$	-H
F389(a), (b), and (c)	O	-CN	-*tert*-butyl	-H
F390(a), (b), and (c)	O	-CN	-*iso*-propyl	-H
F391(a), (b), and (c)	O	-CN	$-CH_3$	$-CH_3$
F392(a), (b), and (c)	O	-CN	-H	-H
F393(a), (b), and (c)	O	-CN	-H	-Cl
F394(a), (b), and (c)	O	-CN	-H	-Br
F395(a), (b), and (c)	O	-CN	-H	-F
F396(a), (b), and (c)	O	-CN	-H	$-CH_3$
F397(a), (b), and (c)	O	-CN	-H	$-CF_3$
F398(a), (b), and (c)	O	-CN	-H	$-OCH_3$
F399(a), (b), and (c)	O	-CN	-H	$-OCH_2CH_3$
F400(a), (b), and (c)	O	-CN	-H	$-OCF_3$
F401(a), (b), and (c)	O	-CN	-H	-*tert*-butyl
F402(a), (b), and (c)	O	-CN	-H	-*iso*-propyl
F403(a), (b), and (c)	O	-Br	-Br	-H
F404(a), (b), and (c)	O	-Br	-Cl	-H
F405(a), (b), and (c)	O	-Br	-F	-H
F406(a), (b), and (c)	O	-Br	$-CH_3$	-H
F407(a), (b), and (c)	O	-Br	$-CF_3$	-H
F408(a), (b), and (c)	O	-Br	$-OCH_3$	-H
F409(a), (b), and (c)	O	-Br	$-OCH_2CH_3$	-H
F410(a), (b), and (c)	O	-Br	$-OCF_3$	-H
F411(a), (b), and (c)	O	-Br	-*tert*-butyl	-H

F412(a), (b), and (c)	O	-Br	-*iso*-propyl	-H
F413(a), (b), and (c)	O	-Br	$-CH_3$	$-CH_3$
F414(a), (b), and (c)	O	-Br	-H	-H
F415(a), (b), and (c)	O	-Br	-H	-Cl
F416(a), (b), and (c)	O	-Br	-H	-Br
F417(a), (b), and (c)	O	-Br	-H	-F
F418(a), (b), and (c)	O	-Br	-H	$-CH_3$
F419(a), (b), and (c)	O	-Br	-H	$-CF_3$
F420(a), (b), and (c)	O	-Br	-H	$-OCH_3$
F421(a), (b), and (c)	O	-Br	-H	$-OCH_2CH_3$
F422(a), (b), and (c)	O	-Br	-H	$-OCF_3$
F423(a), (b), and (c)	O	-Br	-H	-*tert*-butyl
F424(a), (b), and (c)	O	-Br	-H	-*iso*-propyl
F425(a), (b), and (c)	O	-I	-Cl	-H
F426(a), (b), and (c)	O	-I	-Br	-H
F427(a), (b), and (c)	O	-I	-F	-H
F428(a), (b), and (c)	O	-I	$-CH_3$	-H
F429(a), (b), and (c)	O	-I	$-CF_3$	-H
F430(a), (b), and (c)	O	-I	$-OCH_3$	-H
F431(a), (b), and (c)	O	-I	$-OCH_2CH_3$	-H
F432(a), (b), and (c)	O	-I	$-OCF_3$	-H
F433(a), (b), and (c)	O	-I	-*tert*-butyl	-H
F434(a), (b), and (c)	O	-I	-*iso*-propyl	-H
F435(a), (b), and (c)	O	-I	$-CH_3$	$-CH_3$
F436(a), (b), and (c)	O	-I	-H	-H
F437(a), (b), and (c)	O	-I	-H	-Cl
F438(a), (b), and (c)	O	-I	-H	-Br
F439(a), (b), and (c)	O	-I	-H	-F
F440(a), (b), and (c)	O	-I	-H	$-CH_3$
F441(a), (b), and (c)	O	-I	-H	$-CF_3$
F442(a), (b), and (c)	O	-I	-H	$-OCH_3$
F443(a), (b), and (c)	O	-I	-H	$-OCH_2CH_3$
F444(a), (b), and (c)	O	-I	-H	$-OCF_3$
F445(a), (b), and (c)	O	-I	-H	-*tert*-butyl
F446(a), (b), and (c)	O	-I	-H	-*iso*-propyl
F447(a), (b), and (c)	NH	-H	-Cl	-H
F448(a), (b), and (c)	NH	-H	-Br	-H
F449(a), (b), and (c)	NH	-H	-F	-H
F450(a), (b), and (c)	NH	-H	$-CH_3$	-H
F451(a), (b), and (c)	NH	-H	$-CF_3$	-H
F452(a), (b), and (c)	NH	-H	$-OCH_3$	-H
F453(a), (b), and (c)	NH	-H	$-OCH_2CH_3$	-H
F454(a), (b), and (c)	NH	-H	$-OCF_3$	-H
F455(a), (b), and (c)	NH	-H	-*tert*-butyl	-H
F456(a), (b), and (c)	NH	-H	-*iso*-propyl	-H
F457(a), (b), and (c)	NH	-H	$-CH_3$	$-CH_3$
F458(a), (b), and (c)	NH	-H	-H	-H
F459(a), (b), and (c)	NH	-H	-H	-Cl

F460(a), (b), and (c)	NH	-H	-H	-Br
F461(a), (b), and (c)	NH	-H	-H	-F
F462(a), (b), and (c)	NH	-H	-H	$-CH_3$
F463(a), (b), and (c)	NH	-H	-H	$-CF_3$
F464(a), (b), and (c)	NH	-H	-H	$-OCH_3$
F465(a), (b), and (c)	NH	-H	-H	$-OCH_2CH_3$
F466(a), (b), and (c)	NH	-H	-H	$-OCF_3$
F467(a), (b), and (c)	NH	-H	-H	-*tert*-butyl
F468(a), (b), and (c)	NH	-H	-H	-*iso*-propyl
F469(a), (b), and (c)	NH	-Cl	-Cl	-H
F470(a), (b), and (c)	NH	-Cl	-Br	-H
F471(a), (b), and (c)	NH	-Cl	-F	-H
F472(a), (b), and (c)	NH	-Cl	$-CH_3$	-H
F473(a), (b), and (c)	NH	-Cl	$-CF_3$	-H
F474(a), (b), and (c)	NH	-Cl	$-OCH_3$	-H
F475(a), (b), and (c)	NH	-Cl	$-OCH_2CH_3$	-H
F476(a), (b), and (c)	NH	-Cl	$-OCF_3$	-H
F477(a), (b), and (c)	NH	-Cl	-*tert*-butyl	-H
F478(a), (b), and (c)	NH	-Cl	-*iso*-propyl	-H
F479(a), (b), and (c)	NH	-Cl	$-CH_3$	$-CH_3$
F480(a), (b), and (c)	NH	-Cl	-H	-H
F481(a), (b), and (c)	NH	-Cl	-H	$-CH_3$
F482(a), (b), and (c)	NH	-Cl	-H	-Cl
F483(a), (b), and (c)	NH	-Cl	-H	-Br
F484(a), (b), and (c)	NH	-Cl	-H	-F
F485(a), (b), and (c)	NH	-Cl	-H	$-CF_3$
F486(a), (b), and (c)	NH	-Cl	-H	$-OCH_3$
F487(a), (b), and (c)	NH	-Cl	-H	$-OCH_2CH_3$
F488(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
F489(a), (b), and (c)	NH	-Cl	-H	-*tert*-butyl
F490(a), (b), and (c)	NH	-Cl	-H	-*iso*-propyl
F491(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
F492(a), (b), and (c)	NH	-Cl	-H	-*tert*-butyl
F493(a), (b), and (c)	NH	-Cl	-H	-*iso*-propyl
F494(a), (b), and (c)	NH	$-CH_3$	-Cl	-H
F495(a), (b), and (c)	NH	$-CH_3$	-Br	-H
F496(a), (b), and (c)	NH	$-CH_3$	-F	-H
F497(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	-H
F498(a), (b), and (c)	NH	$-CH_3$	$-CF_3$	-H
F499(a), (b), and (c)	NH	$-CH_3$	$-OCH_3$	-H
F500(a), (b), and (c)	NH	$-CH_3$	$-OCH_2CH_3$	-H
F501(a), (b), and (c)	NH	$-CH_3$	$-OCF_3$	-H
F502(a), (b), and (c)	NH	$-CH_3$	-*tert*-butyl	-H
F503(a), (b), and (c)	NH	$-CH_3$	-*iso*-propyl	-H
F504(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	$-CH_3$
F505(a), (b), and (c)	NH	$-CH_3$	-H	-H
F506(a), (b), and (c)	NH	$-CH_3$	-H	-Cl
F507(a), (b), and (c)	NH	$-CH_3$	-H	-Br

F508(a), (b), and (c)	NH	$-CH_3$	-H	-F
F509(a), (b), and (c)	NH	$-CH_3$	-H	$-CH_3$
F510(a), (b), and (c)	NH	$-CH_3$	-H	$-CF_3$
F511(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_3$
F512(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_2CH_3$
F513(a), (b), and (c)	NH	$-CH_3$	-H	$-OCF_3$
F514(a), (b), and (c)	NH	$-CH_3$	-H	*-tert*-butyl
F515(a), (b), and (c)	NH	$-CH_3$	-H	*-iso*-propyl
F516(a), (b), and (c)	NH	$-CF_3$	-Cl	-H
F517(a), (b), and (c)	NH	$-CF_3$	-Br	-H
F518(a), (b), and (c)	NH	$-CF_3$	-F	-H
F519(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	-H
F520(a), (b), and (c)	NH	$-CF_3$	$-CF_3$	-H
F521(a), (b), and (c)	NH	$-CF_3$	$-OCH_3$	-H
F522(a), (b), and (c)	NH	$-CF_3$	$-OCH_2CH_3$	-H
F523(a), (b), and (c)	NH	$-CF_3$	$-OCF_3$	-H
F524(a), (b), and (c)	NH	$-CF_3$	*-tert*-butyl	-H
F525(a), (b), and (c)	NH	$-CF_3$	*-iso*-propyl	-H
F526(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	$-CH_3$
F527(a), (b), and (c)	NH	$-CF_3$	-H	-H
F528(a), (b), and (c)	NH	$-CF_3$	-H	-Cl
F529(a), (b), and (c)	NH	$-CF_3$	-H	-Br
F530(a), (b), and (c)	NH	$-CF_3$	-H	-F
F531(a), (b), and (c)	NH	$-CF_3$	-H	$-CH_3$
F532(a), (b), and (c)	NH	$-CF_3$	-H	$-CF_3$
F533(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_3$
F534(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_2CH_3$
F535(a), (b), and (c)	NH	$-CF_3$	-H	$-OCF_3$
F536(a), (b), and (c)	NH	$-CF_3$	-H	*-tert*-butyl
F537(a), (b), and (c)	NH	$-CF_3$	-H	*-iso*-propyl
F538(a), (b), and (c)	NH	$-CHF_2$	-Cl	-H
F539(a), (b), and (c)	NH	$-CHF_2$	-Br	-H
F540(a), (b), and (c)	NH	$-CHF_2$	-F	-H
F541(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	-H
F542(a), (b), and (c)	NH	$-CHF_2$	$-CF_3$	-H
F543(a), (b), and (c)	NH	$-CHF_2$	$-OCH_3$	-H
F544(a), (b), and (c)	NH	$-CHF_2$	$-OCH_2CH_3$	-H
F545(a), (b), and (c)	NH	$-CHF_2$	$-OCF_3$	-H
F546(a), (b), and (c)	NH	$-CHF_2$	*-tert*-butyl	-H
F547(a), (b), and (c)	NH	$-CHF_2$	*-iso*-propyl	-H
F548(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	$-CH_3$
F549(a), (b), and (c)	NH	$-CHF_2$	-H	-H
F550(a), (b), and (c)	NH	$-CHF_2$	-H	-Cl
F551(a), (b), and (c)	NH	$-CHF_2$	-H	-Br
F552(a), (b), and (c)	NH	$-CHF_2$	-H	-F
F553(a), (b), and (c)	NH	$-CHF_2$	-H	$-CH_3$
F554(a), (b), and (c)	NH	$-CHF_2$	-H	$-CF_3$
F555(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_3$

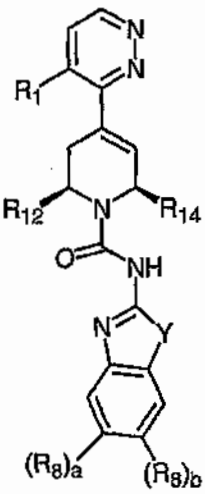
F556(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_2CH_3$
F557(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCF_3$
F558(a), (b), and (c)	NH	$-CHF_2$	-H	*-tert*-butyl
F559(a), (b), and (c)	NH	$-CHF_2$	-H	*-iso*-propyl
F560(a), (b), and (c)	NH	-OH	-Cl	-H
F561(a), (b), and (c)	NH	-OH	-Br	-H
F562(a), (b), and (c)	NH	-OH	-F	-H
F563(a), (b), and (c)	NH	-OH	$-CH_3$	-H
F564(a), (b), and (c)	NH	-OH	$-CF_3$	-H
F565(a), (b), and (c)	NH	-OH	$-OCH_3$	-H
F566(a), (b), and (c)	NH	-OH	$-OCH_2CH_3$	-H
F567(a), (b), and (c)	NH	-OH	$-OCF_3$	-H
F568(a), (b), and (c)	NH	-OH	*-tert*-butyl	-H
F569(a), (b), and (c)	NH	-OH	*-iso*-propyl	-H
F570(a), (b), and (c)	NH	-OH	$-CH_3$	$-CH_3$
F571(a), (b), and (c)	NH	-OH	-H	-H
F572(a), (b), and (c)	NH	-OH	-H	-Cl
F573(a), (b), and (c)	NH	-OH	-H	-Br
F574(a), (b), and (c)	NH	-OH	-H	-F
F575(a), (b), and (c)	NH	-OH	-H	$-CH_3$
F576(a), (b), and (c)	NH	-OH	-H	$-CF_3$
F577(a), (b), and (c)	NH	-OH	-H	$-OCH_3$
F578(a), (b), and (c)	NH	-OH	-H	$-OCH_2CH_3$
F579(a), (b), and (c)	NH	-OH	-H	$-OCF_3$
F580(a), (b), and (c)	NH	-OH	-H	*-tert*-butyl
F581(a), (b), and (c)	NH	-OH	-H	*-iso*-propyl
F582(a), (b), and (c)	NH	$-NO_2$	-Cl	-H
F583(a), (b), and (c)	NH	$-NO_2$	-Br	-H
F584(a), (b), and (c)	NH	$-NO_2$	-F	-H
F585(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	-H
F586(a), (b), and (c)	NH	$-NO_2$	$-CF_3$	-H
F587(a), (b), and (c)	NH	$-NO_2$	$-OCH_3$	-H
F588(a), (b), and (c)	NH	$-NO_2$	$-OCH_2CH_3$	-H
F589(a), (b), and (c)	NH	$-NO_2$	$-OCF_3$	-H
F590(a), (b), and (c)	NH	$-NO_2$	*-tert*-butyl	-H
F591(a), (b), and (c)	NH	$-NO_2$	*-iso*-propyl	-H
F592(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	$-CH_3$
F593(a), (b), and (c)	NH	$-NO_2$	-H	-H
F594(a), (b), and (c)	NH	$-NO_2$	-H	-Cl
F595(a), (b), and (c)	NH	$-NO_2$	-H	-Br
F596(a), (b), and (c)	NH	$-NO_2$	-H	-F
F597(a), (b), and (c)	NH	$-NO_2$	-H	$-CH_3$
F598(a), (b), and (c)	NH	$-NO_2$	-H	$-CF_3$
F599(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_3$
F600(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_2CH_3$
F601(a), (b), and (c)	NH	$-NO_2$	-H	$-OCF_3$
F602(a), (b), and (c)	NH	$-NO_2$	-H	*-tert*-butyl
F603(a), (b), and (c)	NH	$-NO_2$	-H	*-iso*-propyl

F604(a), (b), and (c)	NH	-CN	-Br	-H
F605(a), (b), and (c)	NH	-CN	-Cl	-H
F606(a), (b), and (c)	NH	-CN	-F	-H
F607(a), (b), and (c)	NH	-CN	$-CH_3$	-H
F608(a), (b), and (c)	NH	-CN	$-CF_3$	-H
F609(a), (b), and (c)	NH	-CN	$-OCH_3$	-H
F610(a), (b), and (c)	NH	-CN	$-OCH_2CH_3$	-H
F611(a), (b), and (c)	NH	-CN	$-OCF_3$	-H
F612(a), (b), and (c)	NH	-CN	-*tert*-butyl	-H
F613(a), (b), and (c)	NH	-CN	-*iso*-propyl	-H
F614(a), (b), and (c)	NH	-CN	$-CH_3$	$-CH_3$
F615(a), (b), and (c)	NH	-CN	-H	-H
F616(a), (b), and (c)	NH	-CN	-H	-Cl
F617(a), (b), and (c)	NH	-CN	-H	-Br
F618(a), (b), and (c)	NH	-CN	-H	-F
F619(a), (b), and (c)	NH	-CN	-H	$-CH_3$
F620(a), (b), and (c)	NH	-CN	-H	$-CF_3$
F621(a), (b), and (c)	NH	-CN	-H	$-OCH_3$
F622(a), (b), and (c)	NH	-CN	-H	$-OCH_2CH_3$
F623(a), (b), and (c)	NH	-CN	-H	$-OCF_3$
F624(a), (b), and (c)	NH	-CN	-H	-*tert*-butyl
F625(a), (b), and (c)	NH	-CN	-H	-*iso*-propyl
F626(a), (b), and (c)	NH	-Br	-Br	-H
F627(a), (b), and (c)	NH	-Br	-Cl	-H
F628(a), (b), and (c)	NH	-Br	-F	-H
F629(a), (b), and (c)	NH	-Br	$-CH_3$	-H
F630(a), (b), and (c)	NH	-Br	$-CF_3$	-H
F631(a), (b), and (c)	NH	-Br	$-OCH_3$	-H
F632(a), (b), and (c)	NH	-Br	$-OCH_2CH_3$	-H
F633(a), (b), and (c)	NH	-Br	$-OCF_3$	-H
F634(a), (b), and (c)	NH	-Br	-*tert*-butyl	-H
F635(a), (b), and (c)	NH	-Br	-*iso*-propyl	-H
F636(a), (b), and (c)	NH	-Br	$-CH_3$	$-CH_3$
F637(a), (b), and (c)	NH	-Br	-H	-H
F638(a), (b), and (c)	NH	-Br	-H	-Cl
F639(a), (b), and (c)	NH	-Br	-H	-Br
F640(a), (b), and (c)	NH	-Br	-H	-F
F641(a), (b), and (c)	NH	-Br	-H	$-CH_3$
F642(a), (b), and (c)	NH	-Br	-H	$-CF_3$
F643(a), (b), and (c)	NH	-Br	-H	$-OCH_3$
F644(a), (b), and (c)	NH	-Br	-H	$-OCH_2CH_3$
F645(a), (b), and (c)	NH	-Br	-H	$-OCF_3$
F646(a), (b), and (c)	NH	-Br	-H	-*tert*-butyl
F647(a), (b), and (c)	NH	-Br	-H	-*iso*-propyl
F648(a), (b), and (c)	NH	-I	-Cl	-H
F649(a), (b), and (c)	NH	-I	-Br	-H
F650(a), (b), and (c)	NH	-I	-F	-H
F651(a), (b), and (c)	NH	-I	$-CH_3$	-H

F652(a), (b), and (c)	NH	-I	$-CF_3$	-H
F653(a), (b), and (c)	NH	-I	$-OCH_3$	-H
F654(a), (b), and (c)	NH	-I	$-OCH_2CH_3$	-H
F655(a), (b), and (c)	NH	-I	$-OCF_3$	-H
F656(a), (b), and (c)	NH	-I	*-tert*-butyl	-H
F657(a), (b), and (c)	NH	-I	*-iso*-propyl	-H
F658(a), (b), and (c)	NH	-I	$-CH_3$	$-CH_3$
F659(a), (b), and (c)	NH	-I	-H	-H
F660(a), (b), and (c)	NH	-I	-H	-Cl
F661(a), (b), and (c)	NH	-I	-H	-Br
F662(a), (b), and (c)	NH	-I	-H	-F
F663(a), (b), and (c)	NH	-I	-H	$-CH_3$
F664(a), (b), and (c)	NH	-I	-H	$-CF_3$
F665(a), (b), and (c)	NH	-I	-H	$-OCH_3$
F666(a), (b), and (c)	NH	-I	-H	$-OCH_2CH_3$
F667(a), (b), and (c)	NH	-I	-H	$-OCF_3$
F668(a), (b), and (c)	NH	-I	-H	*-tert*-butyl
F669(a), (b), and (c)	NH	-I	-H	*-iso*-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 7



(Ig)

and pharmaceutically acceptable salts thereof, where:

Compound	Y	R_1	$(R_8)_a$	$(R_8)_b$
G01(a), (b), and (c)	S	-H	-Cl	-H
G02(a), (b), and (c)	S	-H	-Br	-H
G03(a), (b), and (c)	S	-H	-F	-H
G04(a), (b), and (c)	S	-H	$-CH_3$	-H
G05(a), (b), and (c)	S	-H	$-CF_3$	-H
G06(a), (b), and (c)	S	-H	$-OCH_3$	-H
G07(a), (b), and (c)	S	-H	$-OCH_2CH_3$	-H
G08(a), (b), and (c)	S	-H	$-OCF_3$	-H
G09(a), (b), and (c)	S	-H	-*tert*-butyl	-H
G10(a), (b), and (c)	S	-H	-*iso*-propyl	-H
G11(a), (b), and (c)	S	-H	$-CH_3$	$-CH_3$
G12(a), (b), and (c)	S	-H	-H	-H
G13(a), (b), and (c)	S	-H	-H	-Cl
G14(a), (b), and (c)	S	-H	-H	-Br
G15(a), (b), and (c)	S	-H	-H	-F
G16(a), (b), and (c)	S	-H	-H	$-CH_3$
G17(a), (b), and (c)	S	-H	-H	$-CF_3$
G18(a), (b), and (c)	S	-H	-H	$-OCH_3$
G19(a), (b), and (c)	S	-H	-H	$-OCH_2CH_3$
G20(a), (b), and (c)	S	-H	-H	$-OCF_3$
G21(a), (b), and (c)	S	-H	-H	-*tert*-butyl
G22(a), (b), and (c)	S	-H	-H	-*iso*-propyl
G23(a), (b), and (c)	S	-Cl	-Cl	-H
G24(a), (b), and (c)	S	-Cl	-Br	-H
G25(a), (b), and (c)	S	-Cl	-F	-H
G26(a), (b), and (c)	S	-Cl	$-CH_3$	-H

G27(a), (b), and (c)	S	-Cl	$-CF_3$	-H
G28(a), (b), and (c)	S	-Cl	$-OCH_3$	-H
G29(a), (b), and (c)	S	-Cl	$-OCH_2CH_3$	-H
G30(a), (b), and (c)	S	-Cl	$-OCF_3$	-H
G31(a), (b), and (c)	S	-Cl	-*tert*-butyl	-H
G32(a), (b), and (c)	S	-Cl	-*iso*-propyl	-H
G33(a), (b), and (c)	S	-Cl	$-CH_3$	$-CH_3$
G34(a), (b), and (c)	S	-Cl	-H	-H
G35(a), (b), and (c)	S	-Cl	-H	-Cl
G36(a), (b), and (c)	S	-Cl	-H	-Br
G37(a), (b), and (c)	S	-Cl	-H	-F
G38(a), (b), and (c)	S	-Cl	-H	$-CH_3$
G39(a), (b), and (c)	S	-Cl	-H	$-CF_3$
G40(a), (b), and (c)	S	-Cl	-H	$-OCH_3$
G41(a), (b), and (c)	S	-Cl	-H	$-OCH_2CH_3$
G42(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
G43(a), (b), and (c)	S	-Cl	-H	-*tert*-butyl
G44(a), (b), and (c)	S	-Cl	-H	-*iso*-propyl
G45(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
G46(a), (b), and (c)	S	-Cl	-H	-*tert*-butyl
G47(a), (b), and (c)	S	-Cl	-H	-*iso*-propyl
G48(a), (b), and (c)	S	$-CH_3$	-Cl	-H
G49(a), (b), and (c)	S	$-CH_3$	-Br	-H
G50(a), (b), and (c)	S	$-CH_3$	-F	-H
G51(a), (b), and (c)	S	$-CH_3$	$-CH_3$	-H
G52(a), (b), and (c)	S	$-CH_3$	$-CF_3$	-H
G53(a), (b), and (c)	S	$-CH_3$	$-OCH_3$	-H
G54(a), (b), and (c)	S	$-CH_3$	$-OCH_2CH_3$	-H
G55(a), (b), and (c)	S	$-CH_3$	$-OCF_3$	-H
G56(a), (b), and (c)	S	$-CH_3$	-*tert*-butyl	-H
G57(a), (b), and (c)	S	$-CH_3$	-*iso*-propyl	-H
G58(a), (b), and (c)	S	$-CH_3$	$-CH_3$	$-CH_3$
G59(a), (b), and (c)	S	$-CH_3$	-H	-H
G60(a), (b), and (c)	S	$-CH_3$	-H	-Cl
G61(a), (b), and (c)	S	$-CH_3$	-H	-Br
G62(a), (b), and (c)	S	$-CH_3$	-H	-F
G63(a), (b), and (c)	S	$-CH_3$	-H	$-CH_3$
G64(a), (b), and (c)	S	$-CH_3$	-H	$-CF_3$
G65(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_3$
G66(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_2CH_3$
G67(a), (b), and (c)	S	$-CH_3$	-H	$-OCF_3$
G68(a), (b), and (c)	S	$-CH_3$	-H	-*tert*-butyl
G69(a), (b), and (c)	S	$-CH_3$	-H	-*iso*-propyl
G70(a), (b), and (c)	S	$-CF_3$	-Cl	-H
G71(a), (b), and (c)	S	$-CF_3$	-Br	-H
G72(a), (b), and (c)	S	$-CF_3$	-F	-H
G73(a), (b), and (c)	S	$-CF_3$	$-CH_3$	-H
G74(a), (b), and (c)	S	$-CF_3$	$-CF_3$	-H

G75(a), (b), and (c)	S	$-CF_3$	$-OCH_3$	-H
G76(a), (b), and (c)	S	$-CF_3$	$-OCH_2CH_3$	-H
G77(a), (b), and (c)	S	$-CF_3$	$-OCF_3$	-H
G78(a), (b), and (c)	S	$-CF_3$	-*tert*-butyl	-H
G79(a), (b), and (c)	S	$-CF_3$	-*iso*-propyl	-H
G80(a), (b), and (c)	S	$-CF_3$	$-CH_3$	$-CH_3$
G81(a), (b), and (c)	S	$-CF_3$	-H	-H
G82(a), (b), and (c)	S	$-CF_3$	-H	-Cl
G83(a), (b), and (c)	S	$-CF_3$	-H	-Br
G84(a), (b), and (c)	S	$-CF_3$	-H	-F
G85(a), (b), and (c)	S	$-CF_3$	-H	$-CH_3$
G86(a), (b), and (c)	S	$-CF_3$	-H	$-CF_3$
G87(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_3$
G88(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_2CH_3$
G89(a), (b), and (c)	S	$-CF_3$	-H	$-OCF_3$
G90(a), (b), and (c)	S	$-CF_3$	-H	-*tert*-butyl
G91(a), (b), and (c)	S	$-CF_3$	-H	-*iso*-propyl
G92(a), (b), and (c)	S	$-CHF_2$	-Cl	-H
G93(a), (b), and (c)	S	$-CHF_2$	-Br	-H
G94(a), (b), and (c)	S	$-CHF_2$	-F	-H
G95(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	-H
G96(a), (b), and (c)	S	$-CHF_2$	$-CF_3$	-H
G97(a), (b), and (c)	S	$-CHF_2$	$-OCH_3$	-H
G98(a), (b), and (c)	S	$-CHF_2$	$-OCH_2CH_3$	-H
G99(a), (b), and (c)	S	$-CHF_2$	$-OCF_3$	-H
G100(a), (b), and (c)	S	$-CHF_2$	-*tert*-butyl	-H
G101(a), (b), and (c)	S	$-CHF_2$	-*iso*-propyl	-H
G102(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	$-CH_3$
G103(a), (b), and (c)	S	$-CHF_2$	-H	-H
G104(a), (b), and (c)	S	$-CHF_2$	-H	-Cl
G105(a), (b), and (c)	S	$-CHF_2$	-H	-Br
G106(a), (b), and (c)	S	$-CHF_2$	-H	-F
G107(a), (b), and (c)	S	$-CHF_2$	-H	$-CH_3$
G108(a), (b), and (c)	S	$-CHF_2$	-H	$-CF_3$
G109(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_3$
G110(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_2CH_3$
G111(a), (b), and (c)	S	$-CHF_2$	-H	$-OCF_3$
G112(a), (b), and (c)	S	$-CHF_2$	-H	-*tert*-butyl
G113(a), (b), and (c)	S	$-CHF_2$	-H	-*iso*-propyl
G114(a), (b), and (c)	S	-OH	-Cl	-H
G115(a), (b), and (c)	S	-OH	-Br	-H
G116(a), (b), and (c)	S	-OH	-F	-H
G117(a), (b), and (c)	S	-OH	$-CH_3$	-H
G118(a), (b), and (c)	S	-OH	$-CF_3$	-H
G119(a), (b), and (c)	S	-OH	$-OCH_3$	-H
G120(a), (b), and (c)	S	-OH	$-OCH_2CH_3$	-H
G121(a), (b), and (c)	S	-OH	$-OCF_3$	-H
G122(a), (b), and (c)	S	-OH	-*tert*-butyl	-H

G123(a), (b), and (c)	S	-OH	-*iso*-propyl	-H
G124(a), (b), and (c)	S	-OH	$-CH_3$	$-CH_3$
G125(a), (b), and (c)	S	-OH	-H	-H
G126(a), (b), and (c)	S	-OH	-H	-Cl
G127(a), (b), and (c)	S	-OH	-H	-Br
G128(a), (b), and (c)	S	-OH	-H	-F
G129(a), (b), and (c)	S	-OH	-H	$-CH_3$
G130(a), (b), and (c)	S	-OH	-H	$-CF_3$
G131(a), (b), and (c)	S	-OH	-H	$-OCH_3$
G132(a), (b), and (c)	S	-OH	-H	$-OCH_2CH_3$
G133(a), (b), and (c)	S	-OH	-H	$-OCF_3$
G134(a), (b), and (c)	S	-OH	-H	-*tert*-butyl
G135(a), (b), and (c)	S	-OH	-H	-*iso*-propyl
G136(a), (b), and (c)	S	$-NO_2$	-Cl	-H
G137(a), (b), and (c)	S	$-NO_2$	-Br	-H
G138(a), (b), and (c)	S	$-NO_2$	-F	-H
G139(a), (b), and (c)	S	$-NO_2$	$-CH_3$	-H
G140(a), (b), and (c)	S	$-NO_2$	$-CF_3$	-H
G141(a), (b), and (c)	S	$-NO_2$	$-OCH_3$	-H
G142(a), (b), and (c)	S	$-NO_2$	$-OCH_2CH_3$	-H
G143(a), (b), and (c)	S	$-NO_2$	$-OCF_3$	-H
G144(a), (b), and (c)	S	$-NO_2$	-*tert*-butyl	-H
G145(a), (b), and (c)	S	$-NO_2$	-*iso*-propyl	-H
G146(a), (b), and (c)	S	$-NO_2$	$-CH_3$	$-CH_3$
G147(a), (b), and (c)	S	$-NO_2$	-H	-H
G148(a), (b), and (c)	S	$-NO_2$	-H	-Cl
G149(a), (b), and (c)	S	$-NO_2$	-H	-Br
G150(a), (b), and (c)	S	$-NO_2$	-H	-F
G151(a), (b), and (c)	S	$-NO_2$	-H	$-CH_3$
G152(a), (b), and (c)	S	$-NO_2$	-H	$-CF_3$
G153(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_3$
G154(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_2CH_3$
G155(a), (b), and (c)	S	$-NO_2$	-H	$-OCF_3$
G156(a), (b), and (c)	S	$-NO_2$	-H	-*tert*-butyl
G157(a), (b), and (c)	S	$-NO_2$	-H	-*iso*-propyl
G158(a), (b), and (c)	S	-CN	-Br	-H
G159(a), (b), and (c)	S	-CN	-Cl	-H
G160(a), (b), and (c)	S	-CN	-F	-H
G161(a), (b), and (c)	S	-CN	$-CH_3$	-H
G162(a), (b), and (c)	S	-CN	$-CF_3$	-H
G163(a), (b), and (c)	S	-CN	$-OCH_3$	-H
G164(a), (b), and (c)	S	-CN	$-OCH_2CH_3$	-H
G165(a), (b), and (c)	S	-CN	$-OCF_3$	-H
G166(a), (b), and (c)	S	-CN	-*tert*-butyl	-H
G167(a), (b), and (c)	S	-CN	-*iso*-propyl	-H
G168(a), (b), and (c)	S	-CN	$-CH_3$	$-CH_3$
G169(a), (b), and (c)	S	-CN	-H	-H
G170(a), (b), and (c)	S	-CN	-H	-Cl

G171(a), (b), and (c)	S	-CN	-H	-Br
G172(a), (b), and (c)	S	-CN	-H	-F
G173(a), (b), and (c)	S	-CN	-H	$-CH_3$
G174(a), (b), and (c)	S	-CN	-H	$-CF_3$
G175(a), (b), and (c)	S	-CN	-H	$-OCH_3$
G176(a), (b), and (c)	S	-CN	-H	$-OCH_2CH_3$
G177(a), (b), and (c)	S	-CN	-H	$-OCF_3$
G178(a), (b), and (c)	S	-CN	-H	-*tert*-butyl
G179(a), (b), and (c)	S	-CN	-H	-*iso*-propyl
G180(a), (b), and (c)	S	-Br	-Br	-H
G181(a), (b), and (c)	S	-Br	-Cl	-H
G182(a), (b), and (c)	S	-Br	-F	-H
G183(a), (b), and (c)	S	-Br	$-CH_3$	-H
G184(a), (b), and (c)	S	-Br	$-CF_3$	-H
G185(a), (b), and (c)	S	-Br	$-OCH_3$	-H
G186(a), (b), and (c)	S	-Br	$-OCH_2CH_3$	-H
G187(a), (b), and (c)	S	-Br	$-OCF_3$	-H
G188(a), (b), and (c)	S	-Br	-*tert*-butyl	-H
G189(a), (b), and (c)	S	-Br	-*iso*-propyl	-H
G190(a), (b), and (c)	S	-Br	$-CH_3$	$-CH_3$
G191(a), (b), and (c)	S	-Br	-H	-H
G192(a), (b), and (c)	S	-Br	-H	-Cl
G193(a), (b), and (c)	S	-Br	-H	-Br
G194(a), (b), and (c)	S	-Br	-H	-F
G195(a), (b), and (c)	S	-Br	-H	$-CH_3$
G196(a), (b), and (c)	S	-Br	-H	$-CF_3$
G197(a), (b), and (c)	S	-Br	-H	$-OCH_3$
G198(a), (b), and (c)	S	-Br	-H	$-OCH_2CH_3$
G199(a), (b), and (c)	S	-Br	-H	$-OCF_3$
G200(a), (b), and (c)	S	-Br	-H	-*tert*-butyl
G201(a), (b), and (c)	S	-Br	-H	-*iso*-propyl
G202(a), (b), and (c)	S	-I	-Cl	-H
G203(a), (b), and (c)	S	-I	-Br	-H
G204(a), (b), and (c)	S	-I	-F	-H
G205(a), (b), and (c)	S	-I	$-CH_3$	-H
G206(a), (b), and (c)	S	-I	$-CF_3$	-H
G207(a), (b), and (c)	S	-I	$-OCH_3$	-H
G208(a), (b), and (c)	S	-I	$-OCH_2CH_3$	-H
G209(a), (b), and (c)	S	-I	$-OCF_3$	-H
G210(a), (b), and (c)	S	-I	-*tert*-butyl	-H
G211(a), (b), and (c)	S	-I	-*iso*-propyl	-H
G212(a), (b), and (c)	S	-I	$-CH_3$	$-CH_3$
G213(a), (b), and (c)	S	-I	-H	-H
G214(a), (b), and (c)	S	-I	-H	-Cl
G215(a), (b), and (c)	S	-I	-H	-Br
G216(a), (b), and (c)	S	-I	-H	-F
G217(a), (b), and (c)	S	-I	-H	$-CH_3$
G218(a), (b), and (c)	S	-I	-H	$-CF_3$

G219(a), (b), and (c)	S	-I	-H	$-OCH_3$
G220(a), (b), and (c)	S	-I	-H	$-OCH_2CH_3$
G221(a), (b), and (c)	S	-I	-H	$-OCF_3$
G222(a), (b), and (c)	S	-I	-H	*-tert*-butyl
G223(a), (b), and (c)	S	-I	-H	*-iso*-propyl
G224(a), (b), and (c)	O	-H	-Cl	-H
G225(a), (b), and (c)	O	-H	-Br	-H
G226(a), (b), and (c)	O	-H	-F	-H
G227(a), (b), and (c)	O	-H	$-CH_3$	-H
G228(a), (b), and (c)	O	-H	$-CF_3$	-H
G229(a), (b), and (c)	O	-H	$-OCH_3$	-H
G230(a), (b), and (c)	O	-H	$-OCH_2CH_3$	-H
G231(a), (b), and (c)	O	-H	$-OCF_3$	-H
G232(a), (b), and (c)	O	-H	*-tert*-butyl	-H
G233(a), (b), and (c)	O	-H	*-iso*-propyl	-H
G234(a), (b), and (c)	O	-H	$-CH_3$	$-CH_3$
G235(a), (b), and (c)	O	-H	-H	-H
G236(a), (b), and (c)	O	-H	-H	-Cl
G237(a), (b), and (c)	O	-H	-H	-Br
G238(a), (b), and (c)	O	-H	-H	-F
G239(a), (b), and (c)	O	-H	-H	$-CH_3$
G240(a), (b), and (c)	O	-H	-H	$-CF_3$
G241(a), (b), and (c)	O	-H	-H	$-OCH_3$
G242(a), (b), and (c)	O	-H	-H	$-OCH_2CH_3$
G243(a), (b), and (c)	O	-H	-H	$-OCF_3$
G244(a), (b), and (c)	O	-H	-H	*-tert*-butyl
G245(a), (b), and (c)	O	-H	-H	*-iso*-propyl
G246(a), (b), and (c)	O	-Cl	-Cl	-H
G247(a), (b), and (c)	O	-Cl	-Br	-H
G248(a), (b), and (c)	O	-Cl	-F	-H
G249(a), (b), and (c)	O	-Cl	$-CH_3$	-H
G250(a), (b), and (c)	O	-Cl	$-CF_3$	-H
G251(a), (b), and (c)	O	-Cl	$-OCH_3$	-H
G252(a), (b), and (c)	O	-Cl	$-OCH_2CH_3$	-H
G253(a), (b), and (c)	O	-Cl	$-OCF_3$	-H
G254(a), (b), and (c)	O	-Cl	*-tert*-butyl	-H
G255(a), (b), and (c)	O	-Cl	*-iso*-propyl	-H
G256(a), (b), and (c)	O	-Cl	$-CH_3$	$-CH_3$
G257(a), (b), and (c)	O	-Cl	-H	-H
G258(a), (b), and (c)	O	-Cl	-H	$-CH_3$
G259(a), (b), and (c)	O	-Cl	-H	-Cl
G260(a), (b), and (c)	O	-Cl	-H	-Br
G261(a), (b), and (c)	O	-Cl	-H	-F
G262(a), (b), and (c)	O	-Cl	-H	$-CF_3$
G263(a), (b), and (c)	O	-Cl	-H	$-OCH_3$
G264(a), (b), and (c)	O	-Cl	-H	$-OCH_2CH_3$
G265(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
G266(a), (b), and (c)	O	-Cl	-H	*-tert*-butyl

G267(a), (b), and (c)	O	-Cl	-H	-*iso*-propyl
G268(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
G269(a), (b), and (c)	O	-Cl	-H	-*tert*-butyl
G270(a), (b), and (c)	O	-Cl	-H	-*iso*-propyl
G271(a), (b), and (c)	O	$-CH_3$	-Cl	-H
G272(a), (b), and (c)	O	$-CH_3$	-Br	-H
G273(a), (b), and (c)	O	$-CH_3$	-F	-H
G274(a), (b), and (c)	O	$-CH_3$	$-CH_3$	-H
G275(a), (b), and (c)	O	$-CH_3$	$-CF_3$	-H
G276(a), (b), and (c)	O	$-CH_3$	$-OCH_3$	-H
G277(a), (b), and (c)	O	$-CH_3$	$-OCH_2CH_3$	-H
G278(a), (b), and (c)	O	$-CH_3$	$-OCF_3$	-H
G279(a), (b), and (c)	O	$-CH_3$	-*tert*-butyl	-H
G280(a), (b), and (c)	O	$-CH_3$	-*iso*-propyl	-H
G281(a), (b), and (c)	O	$-CH_3$	$-CH_3$	$-CH_3$
G282(a), (b), and (c)	O	$-CH_3$	-H	-H
G283(a), (b), and (c)	O	$-CH_3$	-H	-Cl
G284(a), (b), and (c)	O	$-CH_3$	-H	-Br
G285(a), (b), and (c)	O	$-CH_3$	-H	-F
G286(a), (b), and (c)	O	$-CH_3$	-H	$-CH_3$
G287(a), (b), and (c)	O	$-CH_3$	-H	$-CF_3$
G288(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_3$
G289(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_2CH_3$
G290(a), (b), and (c)	O	$-CH_3$	-H	$-OCF_3$
G291(a), (b), and (c)	O	$-CH_3$	-H	-*tert*-butyl
G292(a), (b), and (c)	O	$-CH_3$	-H	-*iso*-propyl
G293(a), (b), and (c)	O	$-CF_3$	-Cl	-H
G294(a), (b), and (c)	O	$-CF_3$	-Br	-H
G295(a), (b), and (c)	O	$-CF_3$	-F	-H
G296(a), (b), and (c)	O	$-CF_3$	$-CH_3$	-H
G297(a), (b), and (c)	O	$-CF_3$	$-CF_3$	-H
G298(a), (b), and (c)	O	$-CF_3$	$-OCH_3$	-H
G299(a), (b), and (c)	O	$-CF_3$	$-OCH_2CH_3$	-H
G300(a), (b), and (c)	O	$-CF_3$	$-OCF_3$	-H
G301(a), (b), and (c)	O	$-CF_3$	-*tert*-butyl	-H
G302(a), (b), and (c)	O	$-CF_3$	-*iso*-propyl	-H
G303(a), (b), and (c)	O	$-CF_3$	$-CH_3$	$-CH_3$
G304(a), (b), and (c)	O	$-CF_3$	-H	-H
G305(a), (b), and (c)	O	$-CF_3$	-H	-Cl
G306(a), (b), and (c)	O	$-CF_3$	-H	-Br
G307(a), (b), and (c)	O	$-CF_3$	-H	-F
G308(a), (b), and (c)	O	$-CF_3$	-H	$-CH_3$
G309(a), (b), and (c)	O	$-CF_3$	-H	$-CF_3$
G310(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_3$
G311(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_2CH_3$
G312(a), (b), and (c)	O	$-CF_3$	-H	$-OCF_3$
G313(a), (b), and (c)	O	$-CF_3$	-H	-*tert*-butyl
G314(a), (b), and (c)	O	$-CF_3$	-H	-*iso*-propyl

G315(a), (b), and (c)	O	$-CHF_2$	-Cl	-H
G316(a), (b), and (c)	O	$-CHF_2$	-Br	-H
G317(a), (b), and (c)	O	$-CHF_2$	-F	-H
G318(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	-H
G319(a), (b), and (c)	O	$-CHF_2$	$-CF_3$	-H
G320(a), (b), and (c)	O	$-CHF_2$	$-OCH_3$	-H
G321(a), (b), and (c)	O	$-CHF_2$	$-OCH_2CH_3$	-H
G322(a), (b), and (c)	O	$-CHF_2$	$-OCF_3$	-H
G323(a), (b), and (c)	O	$-CHF_2$	-*tert*-butyl	-H
G324(a), (b), and (c)	O	$-CHF_2$	-*iso*-propyl	-H
G325(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	$-CH_3$
G326(a), (b), and (c)	O	$-CHF_2$	-H	-H
G327(a), (b), and (c)	O	$-CHF_2$	-H	-Cl
G328(a), (b), and (c)	O	$-CHF_2$	-H	-Br
G329(a), (b), and (c)	O	$-CHF_2$	-H	-F
G330(a), (b), and (c)	O	$-CHF_2$	-H	$-CH_3$
G331(a), (b), and (c)	O	$-CHF_2$	-H	$-CF_3$
G332(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_3$
G333(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_2CH_3$
G334(a), (b), and (c)	O	$-CHF_2$	-H	$-OCF_3$
G335(a), (b), and (c)	O	$-CHF_2$	-H	-*tert*-butyl
G336(a), (b), and (c)	O	$-CHF_2$	-H	-*iso*-propyl
G337(a), (b), and (c)	O	-OH	-Cl	-H
G338(a), (b), and (c)	O	-OH	-Br	-H
G339(a), (b), and (c)	O	-OH	-F	-H
G340(a), (b), and (c)	O	-OH	$-CH_3$	-H
G341(a), (b), and (c)	O	-OH	$-CF_3$	-H
G342(a), (b), and (c)	O	-OH	$-OCH_3$	-H
G343(a), (b), and (c)	O	-OH	$-OCH_2CH_3$	-H
G344(a), (b), and (c)	O	-OH	$-OCF_3$	-H
G345(a), (b), and (c)	O	-OH	-*tert*-butyl	-H
G346(a), (b), and (c)	O	-OH	-*iso*-propyl	-H
G347(a), (b), and (c)	O	-OH	$-CH_3$	$-CH_3$
G348(a), (b), and (c)	O	-OH	-H	-H
G349(a), (b), and (c)	O	-OH	-H	-Cl
G350(a), (b), and (c)	O	-OH	-H	-Br
G351(a), (b), and (c)	O	-OH	-H	-F
G352(a), (b), and (c)	O	-OH	-H	$-CH_3$
G353(a), (b), and (c)	O	-OH	-H	$-CF_3$
G354(a), (b), and (c)	O	-OH	-H	$-OCH_3$
G355(a), (b), and (c)	O	-OH	-H	$-OCH_2CH_3$
G356(a), (b), and (c)	O	-OH	-H	$-OCF_3$
G357(a), (b), and (c)	O	-OH	-H	-*tert*-butyl
G358(a), (b), and (c)	O	-OH	-H	-*iso*-propyl
G359(a), (b), and (c)	O	$-NO_2$	-Cl	-H
G360(a), (b), and (c)	O	$-NO_2$	-Br	-H
G361(a), (b), and (c)	O	$-NO_2$	-F	-H
G362(a), (b), and (c)	O	$-NO_2$	$-CH_3$	-H

G363(a), (b), and (c)	O	$-NO_2$	$-CF_3$	-H
G364(a), (b), and (c)	O	$-NO_2$	$-OCH_3$	-H
G365(a), (b), and (c)	O	$-NO_2$	$-OCH_2CH_3$	-H
G366(a), (b), and (c)	O	$-NO_2$	$-OCF_3$	-H
G367(a), (b), and (c)	O	$-NO_2$	-*tert*-butyl	-H
G368(a), (b), and (c)	O	$-NO_2$	-*iso*-propyl	-H
G369(a), (b), and (c)	O	$-NO_2$	$-CH_3$	$-CH_3$
G370(a), (b), and (c)	O	$-NO_2$	-H	-H
G371(a), (b), and (c)	O	$-NO_2$	-H	-Cl
G372(a), (b), and (c)	O	$-NO_2$	-H	-Br
G373(a), (b), and (c)	O	$-NO_2$	-H	-F
G374(a), (b), and (c)	O	$-NO_2$	-H	$-CH_3$
G375(a), (b), and (c)	O	$-NO_2$	-H	$-CF_3$
G376(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_3$
G377(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_2CH_3$
G378(a), (b), and (c)	O	$-NO_2$	-H	$-OCF_3$
G379(a), (b), and (c)	O	$-NO_2$	-H	-*tert*-butyl
G380(a), (b), and (c)	O	$-NO_2$	-H	-*iso*-propyl
G381(a), (b), and (c)	O	-CN	-Br	-H
G382(a), (b), and (c)	O	-CN	-Cl	-H
G383(a), (b), and (c)	O	-CN	-F	-H
G384(a), (b), and (c)	O	-CN	$-CH_3$	-H
G385(a), (b), and (c)	O	-CN	$-CF_3$	-H
G386(a), (b), and (c)	O	-CN	$-OCH_3$	-H
G387(a), (b), and (c)	O	-CN	$-OCH_2CH_3$	-H
G388(a), (b), and (c)	O	-CN	$-OCF_3$	-H
G389(a), (b), and (c)	O	-CN	-*tert*-butyl	-H
G390(a), (b), and (c)	O	-CN	-*iso*-propyl	-H
G391(a), (b), and (c)	O	-CN	$-CH_3$	$-CH_3$
G392(a), (b), and (c)	O	-CN	-H	-H
G393(a), (b), and (c)	O	-CN	-H	-Cl
G394(a), (b), and (c)	O	-CN	-H	-Br
G395(a), (b), and (c)	O	-CN	-H	-F
G396(a), (b), and (c)	O	-CN	-H	$-CH_3$
G397(a), (b), and (c)	O	-CN	-H	$-CF_3$
G398(a), (b), and (c)	O	-CN	-H	$-OCH_3$
G399(a), (b), and (c)	O	-CN	-H	$-OCH_2CH_3$
G400(a), (b), and (c)	O	-CN	-H	$-OCF_3$
G401(a), (b), and (c)	O	-CN	-H	-*tert*-butyl
G402(a), (b), and (c)	O	-CN	-H	-*iso*-propyl
G403(a), (b), and (c)	O	-Br	-Br	-H
G404(a), (b), and (c)	O	-Br	-Cl	-H
G405(a), (b), and (c)	O	-Br	-F	-H
G406(a), (b), and (c)	O	-Br	$-CH_3$	-H
G407(a), (b), and (c)	O	-Br	$-CF_3$	-H
G408(a), (b), and (c)	O	-Br	$-OCH_3$	-H
G409(a), (b), and (c)	O	-Br	$-OCH_2CH_3$	-H
G410(a), (b), and (c)	O	-Br	$-OCF_3$	-H

G411(a), (b), and (c)	O	-Br	-*tert*-butyl	-H
G412(a), (b), and (c)	O	-Br	-*iso*-propyl	-H
G413(a), (b), and (c)	O	-Br	$-CH_3$	$-CH_3$
G414(a), (b), and (c)	O	-Br	-H	-H
G415(a), (b), and (c)	O	-Br	-H	-Cl
G416(a), (b), and (c)	O	-Br	-H	-Br
G417(a), (b), and (c)	O	-Br	-H	-F
G418(a), (b), and (c)	O	-Br	-H	$-CH_3$
G419(a), (b), and (c)	O	-Br	-H	$-CF_3$
G420(a), (b), and (c)	O	-Br	-H	$-OCH_3$
G421(a), (b), and (c)	O	-Br	-H	$-OCH_2CH_3$
G422(a), (b), and (c)	O	-Br	-H	$-OCF_3$
G423(a), (b), and (c)	O	-Br	-H	-*tert*-butyl
G424(a), (b), and (c)	O	-Br	-H	-*iso*-propyl
G425(a), (b), and (c)	O	-I	-Cl	-H
G426(a), (b), and (c)	O	-I	-Br	-H
G427(a), (b), and (c)	O	-I	-F	-H
G428(a), (b), and (c)	O	-I	$-CH_3$	-H
G429(a), (b), and (c)	O	-I	$-CF_3$	-H
G430(a), (b), and (c)	O	-I	$-OCH_3$	-H
G431(a), (b), and (c)	O	-I	$-OCH_2CH_3$	-H
G432(a), (b), and (c)	O	-I	$-OCF_3$	-H
G433(a), (b), and (c)	O	-I	-*tert*-butyl	-H
G434(a), (b), and (c)	O	-I	-*iso*-propyl	-H
G435(a), (b), and (c)	O	-I	$-CH_3$	$-CH_3$
G436(a), (b), and (c)	O	-I	-H	-H
G437(a), (b), and (c)	O	-I	-H	-Cl
G438(a), (b), and (c)	O	-I	-H	-Br
G439(a), (b), and (c)	O	-I	-H	-F
G440(a), (b), and (c)	O	-I	-H	$-CH_3$
G441(a), (b), and (c)	O	-I	-H	$-CF_3$
G442(a), (b), and (c)	O	-I	-H	$-OCH_3$
G443(a), (b), and (c)	O	-I	-H	$-OCH_2CH_3$
G444(a), (b), and (c)	O	-I	-H	$-OCF_3$
G445(a), (b), and (c)	O	-I	-H	-*tert*-butyl
G446(a), (b), and (c)	O	-I	-H	-*iso*-propyl
G447(a), (b), and (c)	NH	-H	-Cl	-H
G448(a), (b), and (c)	NH	-H	-Br	-H
G449(a), (b), and (c)	NH	-H	-F	-H
G450(a), (b), and (c)	NH	-H	$-CH_3$	-H
G451(a), (b), and (c)	NH	-H	$-CF_3$	-H
G452(a), (b), and (c)	NH	-H	$-OCH_3$	-H
G453(a), (b), and (c)	NH	-H	$-OCH_2CH_3$	-H
G454(a), (b), and (c)	NH	-H	$-OCF_3$	-H
G455(a), (b), and (c)	NH	-H	-*tert*-butyl	-H
G456(a), (b), and (c)	NH	-H	-*iso*-propyl	-H
G457(a), (b), and (c)	NH	-H	$-CH_3$	$-CH_3$
G458(a), (b), and (c)	NH	-H	-H	-H

G459(a), (b), and (c)	NH	-H	-H	-Cl
G460(a), (b), and (c)	NH	-H	-H	-Br
G461(a), (b), and (c)	NH	-H	-H	-F
G462(a), (b), and (c)	NH	-H	-H	$-CH_3$
G463(a), (b), and (c)	NH	-H	-H	$-CF_3$
G464(a), (b), and (c)	NH	-H	-H	$-OCH_3$
G465(a), (b), and (c)	NH	-H	-H	$-OCH_2CH_3$
G466(a), (b), and (c)	NH	-H	-H	$-OCF_3$
G467(a), (b), and (c)	NH	-H	-H	*-tert*-butyl
G468(a), (b), and (c)	NH	-H	-H	*-iso*-propyl
G469(a), (b), and (c)	NH	-Cl	-Cl	-H
G470(a), (b), and (c)	NH	-Cl	-Br	-H
G471(a), (b), and (c)	NH	-Cl	-F	-H
G472(a), (b), and (c)	NH	-Cl	$-CH_3$	-H
G473(a), (b), and (c)	NH	-Cl	$-CF_3$	-H
G474(a), (b), and (c)	NH	-Cl	$-OCH_3$	-H
G475(a), (b), and (c)	NH	-Cl	$-OCH_2CH_3$	-H
G476(a), (b), and (c)	NH	-Cl	$-OCF_3$	-H
G477(a), (b), and (c)	NH	-Cl	*-tert*-butyl	-H
G478(a), (b), and (c)	NH	-Cl	*-iso*-propyl	-H
G479(a), (b), and (c)	NH	-Cl	$-CH_3$	$-CH_3$
G480(a), (b), and (c)	NH	-Cl	-H	-H
G481(a), (b), and (c)	NH	-Cl	-H	$-CH_3$
G482(a), (b), and (c)	NH	-Cl	-H	-Cl
G483(a), (b), and (c)	NH	-Cl	-H	-Br
G484(a), (b), and (c)	NH	-Cl	-H	-F
G485(a), (b), and (c)	NH	-Cl	-H	$-CF_3$
G486(a), (b), and (c)	NH	-Cl	-H	$-OCH_3$
G487(a), (b), and (c)	NH	-Cl	-H	$-OCH_2CH_3$
G488(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
G489(a), (b), and (c)	NH	-Cl	-H	*-tert*-butyl
G490(a), (b), and (c)	NH	-Cl	-H	*-iso*-propyl
G491(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
G492(a), (b), and (c)	NH	-Cl	-H	*-tert*-butyl
G493(a), (b), and (c)	NH	-Cl	-H	*-iso*-propyl
G494(a), (b), and (c)	NH	$-CH_3$	-Cl	-H
G495(a), (b), and (c)	NH	$-CH_3$	-Br	-H
G496(a), (b), and (c)	NH	$-CH_3$	-F	-H
G497(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	-H
G498(a), (b), and (c)	NH	$-CH_3$	$-CF_3$	-H
G499(a), (b), and (c)	NH	$-CH_3$	$-OCH_3$	-H
G500(a), (b), and (c)	NH	$-CH_3$	$-OCH_2CH_3$	-H
G501(a), (b), and (c)	NH	$-CH_3$	$-OCF_3$	-H
G502(a), (b), and (c)	NH	$-CH_3$	*-tert*-butyl	-H
G503(a), (b), and (c)	NH	$-CH_3$	*-iso*-propyl	-H
G504(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	$-CH_3$
G505(a), (b), and (c)	NH	$-CH_3$	-H	-H
G506(a), (b), and (c)	NH	$-CH_3$	-H	-Cl

G507(a), (b), and (c)	NH	$-CH_3$	-H	-Br
G508(a), (b), and (c)	NH	$-CH_3$	-H	-F
G509(a), (b), and (c)	NH	$-CH_3$	-H	$-CH_3$
G510(a), (b), and (c)	NH	$-CH_3$	-H	$-CF_3$
G511(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_3$
G512(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_2CH_3$
G513(a), (b), and (c)	NH	$-CH_3$	-H	$-OCF_3$
G514(a), (b), and (c)	NH	$-CH_3$	-H	*-tert*-butyl
G515(a), (b), and (c)	NH	$-CH_3$	-H	*-iso*-propyl
G516(a), (b), and (c)	NH	$-CF_3$	-Cl	-H
G517(a), (b), and (c)	NH	$-CF_3$	-Br	-H
G518(a), (b), and (c)	NH	$-CF_3$	-F	-H
G519(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	-H
G520(a), (b), and (c)	NH	$-CF_3$	$-CF_3$	-H
G521(a), (b), and (c)	NH	$-CF_3$	$-OCH_3$	-H
G522(a), (b), and (c)	NH	$-CF_3$	$-OCH_2CH_3$	-H
G523(a), (b), and (c)	NH	$-CF_3$	$-OCF_3$	-H
G524(a), (b), and (c)	NH	$-CF_3$	*-tert*-butyl	-H
G525(a), (b), and (c)	NH	$-CF_3$	*-iso*-propyl	-H
G526(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	$-CH_3$
G527(a), (b), and (c)	NH	$-CF_3$	-H	-H
G528(a), (b), and (c)	NH	$-CF_3$	-H	-Cl
G529(a), (b), and (c)	NH	$-CF_3$	-H	-Br
G530(a), (b), and (c)	NH	$-CF_3$	-H	-F
G531(a), (b), and (c)	NH	$-CF_3$	-H	$-CH_3$
G532(a), (b), and (c)	NH	$-CF_3$	-H	$-CF_3$
G533(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_3$
G534(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_2CH_3$
G535(a), (b), and (c)	NH	$-CF_3$	-H	$-OCF_3$
G536(a), (b), and (c)	NH	$-CF_3$	-H	*-tert*-butyl
G537(a), (b), and (c)	NH	$-CF_3$	-H	*-iso*-propyl
G538(a), (b), and (c)	NH	$-CHF_2$	-Cl	-H
G539(a), (b), and (c)	NH	$-CHF_2$	-Br	-H
G540(a), (b), and (c)	NH	$-CHF_2$	-F	-H
G541(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	-H
G542(a), (b), and (c)	NH	$-CHF_2$	$-CF_3$	-H
G543(a), (b), and (c)	NH	$-CHF_2$	$-OCH_3$	-H
G544(a), (b), and (c)	NH	$-CHF_2$	$-OCH_2CH_3$	-H
G545(a), (b), and (c)	NH	$-CHF_2$	$-OCF_3$	-H
G546(a), (b), and (c)	NH	$-CHF_2$	*-tert*-butyl	-H
G547(a), (b), and (c)	NH	$-CHF_2$	*-iso*-propyl	-H
G548(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	$-CH_3$
G549(a), (b), and (c)	NH	$-CHF_2$	-H	-H
G550(a), (b), and (c)	NH	$-CHF_2$	-H	-Cl
G551(a), (b), and (c)	NH	$-CHF_2$	-H	-Br
G552(a), (b), and (c)	NH	$-CHF_2$	-H	-F
G553(a), (b), and (c)	NH	$-CHF_2$	-H	$-CH_3$
G554(a), (b), and (c)	NH	$-CHF_2$	-H	$-CF_3$

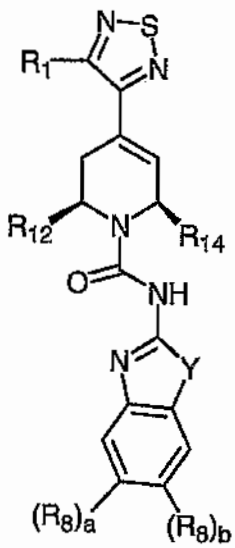
G555(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_3$
G556(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_2CH_3$
G557(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCF_3$
G558(a), (b), and (c)	NH	$-CHF_2$	-H	*-tert*-butyl
G559(a), (b), and (c)	NH	$-CHF_2$	-H	*-iso*-propyl
G560(a), (b), and (c)	NH	-OH	-Cl	-H
G561(a), (b), and (c)	NH	-OH	-Br	-H
G562(a), (b), and (c)	NH	-OH	-F	-H
G563(a), (b), and (c)	NH	-OH	$-CH_3$	-H
G564(a), (b), and (c)	NH	-OH	$-CF_3$	-H
G565(a), (b), and (c)	NH	-OH	$-OCH_3$	-H
G566(a), (b), and (c)	NH	-OH	$-OCH_2CH_3$	-H
G567(a), (b), and (c)	NH	-OH	$-OCF_3$	-H
G568(a), (b), and (c)	NH	-OH	*-tert*-butyl	-H
G569(a), (b), and (c)	NH	-OH	*-iso*-propyl	-H
G570(a), (b), and (c)	NH	-OH	$-CH_3$	$-CH_3$
G571(a), (b), and (c)	NH	-OH	-H	-H
G572(a), (b), and (c)	NH	-OH	-H	-Cl
G573(a), (b), and (c)	NH	-OH	-H	-Br
G574(a), (b), and (c)	NH	-OH	-H	-F
G575(a), (b), and (c)	NH	-OH	-H	$-CH_3$
G576(a), (b), and (c)	NH	-OH	-H	$-CF_3$
G577(a), (b), and (c)	NH	-OH	-H	$-OCH_3$
G578(a), (b), and (c)	NH	-OH	-H	$-OCH_2CH_3$
G579(a), (b), and (c)	NH	-OH	-H	$-OCF_3$
G580(a), (b), and (c)	NH	-OH	-H	*-tert*-butyl
G581(a), (b), and (c)	NH	-OH	-H	*-iso*-propyl
G582(a), (b), and (c)	NH	$-NO_2$	-Cl	-H
G583(a), (b), and (c)	NH	$-NO_2$	-Br	-H
G584(a), (b), and (c)	NH	$-NO_2$	-F	-H
G585(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	-H
G586(a), (b), and (c)	NH	$-NO_2$	$-CF_3$	-H
G587(a), (b), and (c)	NH	$-NO_2$	$-OCH_3$	-H
G588(a), (b), and (c)	NH	$-NO_2$	$-OCH_2CH_3$	-H
G589(a), (b), and (c)	NH	$-NO_2$	$-OCF_3$	-H
G590(a), (b), and (c)	NH	$-NO_2$	*-tert*-butyl	-H
G591(a), (b), and (c)	NH	$-NO_2$	*-iso*-propyl	-H
G592(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	$-CH_3$
G593(a), (b), and (c)	NH	$-NO_2$	-H	-H
G594(a), (b), and (c)	NH	$-NO_2$	-H	-Cl
G595(a), (b), and (c)	NH	$-NO_2$	-H	-Br
G596(a), (b), and (c)	NH	$-NO_2$	-H	-F
G597(a), (b), and (c)	NH	$-NO_2$	-H	$-CH_3$
G598(a), (b), and (c)	NH	$-NO_2$	-H	$-CF_3$
G599(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_3$
G600(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_2CH_3$
G601(a), (b), and (c)	NH	$-NO_2$	-H	$-OCF_3$
G602(a), (b), and (c)	NH	$-NO_2$	-H	*-tert*-butyl

G603(a), (b), and (c)	NH	$-NO_2$	-H	-*iso*-propyl
G604(a), (b), and (c)	NH	-CN	-Br	-H
G605(a), (b), and (c)	NH	-CN	-Cl	-H
G606(a), (b), and (c)	NH	-CN	-F	-H
G607(a), (b), and (c)	NH	-CN	$-CH_3$	-H
G608(a), (b), and (c)	NH	-CN	$-CF_3$	-H
G609(a), (b), and (c)	NH	-CN	$-OCH_3$	-H
G610(a), (b), and (c)	NH	-CN	$-OCH_2CH_3$	-H
G611(a), (b), and (c)	NH	-CN	$-OCF_3$	-H
G612(a), (b), and (c)	NH	-CN	-*tert*-butyl	-H
G613(a), (b), and (c)	NH	-CN	-*iso*-propyl	-H
G614(a), (b), and (c)	NH	-CN	$-CH_3$	$-CH_3$
G615(a), (b), and (c)	NH	-CN	-H	-H
G616(a), (b), and (c)	NH	-CN	-H	-Cl
G617(a), (b), and (c)	NH	-CN	-H	-Br
G618(a), (b), and (c)	NH	-CN	-H	-F
G619(a), (b), and (c)	NH	-CN	-H	$-CH_3$
G620(a), (b), and (c)	NH	-CN	-H	$-CF_3$
G621(a), (b), and (c)	NH	-CN	-H	$-OCH_3$
G622(a), (b), and (c)	NH	-CN	-H	$-OCH_2CH_3$
G623(a), (b), and (c)	NH	-CN	-H	$-OCF_3$
G624(a), (b), and (c)	NH	-CN	-H	-*tert*-butyl
G625(a), (b), and (c)	NH	-CN	-H	-*iso*-propyl
G626(a), (b), and (c)	NH	-Br	-Br	-H
G627(a), (b), and (c)	NH	-Br	-Cl	-H
G628(a), (b), and (c)	NH	-Br	-F	-H
G629(a), (b), and (c)	NH	-Br	$-CH_3$	-H
G630(a), (b), and (c)	NH	-Br	$-CF_3$	-H
G631(a), (b), and (c)	NH	-Br	$-OCH_3$	-H
G632(a), (b), and (c)	NH	-Br	$-OCH_2CH_3$	-H
G633(a), (b), and (c)	NH	-Br	$-OCF_3$	-H
G634(a), (b), and (c)	NH	-Br	-*tert*-butyl	-H
G635(a), (b), and (c)	NH	-Br	-*iso*-propyl	-H
G636(a), (b), and (c)	NH	-Br	$-CH_3$	$-CH_3$
G637(a), (b), and (c)	NH	-Br	-H	-H
G638(a), (b), and (c)	NH	-Br	-H	-Cl
G639(a), (b), and (c)	NH	-Br	-H	-Br
G640(a), (b), and (c)	NH	-Br	-H	-F
G641(a), (b), and (c)	NH	-Br	-H	$-CH_3$
G642(a), (b), and (c)	NH	-Br	-H	$-CF_3$
G643(a), (b), and (c)	NH	-Br	-H	$-OCH_3$
G644(a), (b), and (c)	NH	-Br	-H	$-OCH_2CH_3$
G645(a), (b), and (c)	NH	-Br	-H	$-OCF_3$
G646(a), (b), and (c)	NH	-Br	-H	-*tert*-butyl
G647(a), (b), and (c)	NH	-Br	-H	-*iso*-propyl
G648(a), (b), and (c)	NH	-I	-Cl	-H
G649(a), (b), and (c)	NH	-I	-Br	-H
G650(a), (b), and (c)	NH	-I	-F	-H

G651(a), (b), and (c)	NH	-I	$-CH_3$	-H
G652(a), (b), and (c)	NH	-I	$-CF_3$	-H
G653(a), (b), and (c)	NH	-I	$-OCH_3$	-H
G654(a), (b), and (c)	NH	-I	$-OCH_2CH_3$	-H
G655(a), (b), and (c)	NH	-I	$-OCF_3$	-H
G656(a), (b), and (c)	NH	-I	-*tert*-butyl	-H
G657(a), (b), and (c)	NH	-I	-*iso*-propyl	-H
G658(a), (b), and (c)	NH	-I	$-CH_3$	$-CH_3$
G659(a), (b), and (c)	NH	-I	-H	-H
G660(a), (b), and (c)	NH	-I	-H	-Cl
G661(a), (b), and (c)	NH	-I	-H	-Br
G662(a), (b), and (c)	NH	-I	-H	-F
G663(a), (b), and (c)	NH	-I	-H	$-CH_3$
G664(a), (b), and (c)	NH	-I	-H	$-CF_3$
G665(a), (b), and (c)	NH	-I	-H	$-OCH_3$
G666(a), (b), and (c)	NH	-I	-H	$-OCH_2CH_3$
G667(a), (b), and (c)	NH	-I	-H	$-OCF_3$
G668(a), (b), and (c)	NH	-I	-H	-*tert*-butyl
G669(a), (b), and (c)	NH	-I	-H	-*iso*-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 8



(Ih)

and pharmaceutically acceptable salts thereof, where:

Compound	Y	R_1	$(R_8)_a$	$(R_8)_b$
H01(a), (b), and (c)	S	-H	-Cl	-H
H02(a), (b), and (c)	S	-H	-Br	-H
H03(a), (b), and (c)	S	-H	-F	-H
H04(a), (b), and (c)	S	-H	$-CH_3$	-H
H05(a), (b), and (c)	S	-H	$-CF_3$	-H
H06(a), (b), and (c)	S	-H	$-OCH_3$	-H
H07(a), (b), and (c)	S	-H	$-OCH_2CH_3$	-H
H08(a), (b), and (c)	S	-H	$-OCF_3$	-H
H09(a), (b), and (c)	S	-H	-*tert*-butyl	-H
H10(a), (b), and (c)	S	-H	-*iso*-propyl	-H
H11(a), (b), and (c)	S	-H	$-CH_3$	$-CH_3$
H12(a), (b), and (c)	S	-H	-H	-H
H13(a), (b), and (c)	S	-H	-H	-Cl
H14(a), (b), and (c)	S	-H	-H	-Br
H15(a), (b), and (c)	S	-H	-H	-F
H16(a), (b), and (c)	S	-H	-H	$-CH_3$
H17(a), (b), and (c)	S	-H	-H	$-CF_3$
H18(a), (b), and (c)	S	-H	-H	$-OCH_3$
H19(a), (b), and (c)	S	-H	-H	$-OCH_2CH_3$
H20(a), (b), and (c)	S	-H	-H	$-OCF_3$
H21(a), (b), and (c)	S	-H	-H	-*tert*-butyl
H22(a), (b), and (c)	S	-H	-H	-*iso*-propyl
H23(a), (b), and (c)	S	-Cl	-Cl	-H
H24(a), (b), and (c)	S	-Cl	-Br	-H

H25(a), (b), and (c)	S	-Cl	-F	-H
H26(a), (b), and (c)	S	-Cl	$-CH_3$	-H
H27(a), (b), and (c)	S	-Cl	$-CF_3$	-H
H28(a), (b), and (c)	S	-Cl	$-OCH_3$	-H
H29(a), (b), and (c)	S	-Cl	$-OCH_2CH_3$	-H
H30(a), (b), and (c)	S	-Cl	$-OCF_3$	-H
H31(a), (b), and (c)	S	-Cl	*-tert*-butyl	-H
H32(a), (b), and (c)	S	-Cl	*-iso*-propyl	-H
H33(a), (b), and (c)	S	-Cl	$-CH_3$	$-CH_3$
H34(a), (b), and (c)	S	-Cl	-H	-H
H35(a), (b), and (c)	S	-Cl	-H	-Cl
H36(a), (b), and (c)	S	-Cl	-H	-Br
H37(a), (b), and (c)	S	-Cl	-H	-F
H38(a), (b), and (c)	S	-Cl	-H	$-CH_3$
H39(a), (b), and (c)	S	-Cl	-H	$-CF_3$
H40(a), (b), and (c)	S	-Cl	-H	$-OCH_3$
H41(a), (b), and (c)	S	-Cl	-H	$-OCH_2CH_3$
H42(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
H43(a), (b), and (c)	S	-Cl	-H	*-tert*-butyl
H44(a), (b), and (c)	S	-Cl	-H	*-iso*-propyl
H45(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
H46(a), (b), and (c)	S	-Cl	-H	*-tert*-butyl
H47(a), (b), and (c)	S	-Cl	-H	*-iso*-propyl
H48(a), (b), and (c)	S	$-CH_3$	-Cl	-H
H49(a), (b), and (c)	S	$-CH_3$	-Br	-H
H50(a), (b), and (c)	S	$-CH_3$	-F	-H
H51(a), (b), and (c)	S	$-CH_3$	$-CH_3$	-H
H52(a), (b), and (c)	S	$-CH_3$	$-CF_3$	-H
H53(a), (b), and (c)	S	$-CH_3$	$-OCH_3$	-H
H54(a), (b), and (c)	S	$-CH_3$	$-OCH_2CH_3$	-H
H55(a), (b), and (c)	S	$-CH_3$	$-OCF_3$	-H
H56(a), (b), and (c)	S	$-CH_3$	*-tert*-butyl	-H
H57(a), (b), and (c)	S	$-CH_3$	*-iso*-propyl	-H
H58(a), (b), and (c)	S	$-CH_3$	$-CH_3$	$-CH_3$
H59(a), (b), and (c)	S	$-CH_3$	-H	-H
H60(a), (b), and (c)	S	$-CH_3$	-H	-Cl
H61(a), (b), and (c)	S	$-CH_3$	-H	-Br
H62(a), (b), and (c)	S	$-CH_3$	-H	-F
H63(a), (b), and (c)	S	$-CH_3$	-H	$-CH_3$
H64(a), (b), and (c)	S	$-CH_3$	-H	$-CF_3$
H65(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_3$
H66(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_2CH_3$
H67(a), (b), and (c)	S	$-CH_3$	-H	$-OCF_3$
H68(a), (b), and (c)	S	$-CH_3$	-H	*-tert*-butyl
H69(a), (b), and (c)	S	$-CH_3$	-H	*-iso*-propyl
H70(a), (b), and (c)	S	$-CF_3$	-Cl	-H
H71(a), (b), and (c)	S	$-CF_3$	-Br	-H
H72(a), (b), and (c)	S	$-CF_3$	-F	-H

H73(a), (b), and (c)	S	$-CF_3$	$-CH_3$	-H
H74(a), (b), and (c)	S	$-CF_3$	$-CF_3$	-H
H75(a), (b), and (c)	S	$-CF_3$	$-OCH_3$	-H
H76(a), (b), and (c)	S	$-CF_3$	$-OCH_2CH_3$	-H
H77(a), (b), and (c)	S	$-CF_3$	$-OCF_3$	-H
H78(a), (b), and (c)	S	$-CF_3$	-*tert*-butyl	-H
H79(a), (b), and (c)	S	$-CF_3$	-*iso*-propyl	-H
H80(a), (b), and (c)	S	$-CF_3$	$-CH_3$	$-CH_3$
H81(a), (b), and (c)	S	$-CF_3$	-H	-H
H82(a), (b), and (c)	S	$-CF_3$	-H	-Cl
H83(a), (b), and (c)	S	$-CF_3$	-H	-Br
H84(a), (b), and (c)	S	$-CF_3$	-H	-F
H85(a), (b), and (c)	S	$-CF_3$	-H	$-CH_3$
H86(a), (b), and (c)	S	$-CF_3$	-H	$-CF_3$
H87(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_3$
H88(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_2CH_3$
H89(a), (b), and (c)	S	$-CF_3$	-H	$-OCF_3$
H90(a), (b), and (c)	S	$-CF_3$	-H	-*tert*-butyl
H91(a), (b), and (c)	S	$-CF_3$	-H	-*iso*-propyl
H92(a), (b), and (c)	S	$-CHF_2$	-Cl	-H
H93(a), (b), and (c)	S	$-CHF_2$	-Br	-H
H94(a), (b), and (c)	S	$-CHF_2$	-F	-H
H95(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	-H
H96(a), (b), and (c)	S	$-CHF_2$	$-CF_3$	-H
H97(a), (b), and (c)	S	$-CHF_2$	$-OCH_3$	-H
H98(a), (b), and (c)	S	$-CHF_2$	$-OCH_2CH_3$	-H
H99(a), (b), and (c)	S	$-CHF_2$	$-OCF_3$	-H
H100(a), (b), and (c)	S	$-CHF_2$	-*tert*-butyl	-H
H101(a), (b), and (c)	S	$-CHF_2$	-*iso*-propyl	-H
H102(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	$-CH_3$
H103(a), (b), and (c)	S	$-CHF_2$	-H	-H
H104(a), (b), and (c)	S	$-CHF_2$	-H	-Cl
H105(a), (b), and (c)	S	$-CHF_2$	-H	-Br
H106(a), (b), and (c)	S	$-CHF_2$	-H	-F
H107(a), (b), and (c)	S	$-CHF_2$	-H	$-CH_3$
H108(a), (b), and (c)	S	$-CHF_2$	-H	$-CF_3$
H109(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_3$
H110(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_2CH_3$
H111(a), (b), and (c)	S	$-CHF_2$	-H	$-OCF_3$
H112(a), (b), and (c)	S	$-CHF_2$	-H	-*tert*-butyl
H113(a), (b), and (c)	S	$-CHF_2$	-H	-*iso*-propyl
H114(a), (b), and (c)	S	-OH	-Cl	-H
H115(a), (b), and (c)	S	-OH	-Br	-H
H116(a), (b), and (c)	S	-OH	-F	-H
H117(a), (b), and (c)	S	-OH	$-CH_3$	-H
H118(a), (b), and (c)	S	-OH	$-CF_3$	-H
H119(a), (b), and (c)	S	-OH	$-OCH_3$	-H
H120(a), (b), and (c)	S	-OH	$-OCH_2CH_3$	-H

H121(a), (b), and (c)	S	-OH	$-OCF_3$	-H
H122(a), (b), and (c)	S	-OH	-*tert*-butyl	-H
H123(a), (b), and (c)	S	-OH	-*iso*-propyl	-H
H124(a), (b), and (c)	S	-OH	$-CH_3$	$-CH_3$
H125(a), (b), and (c)	S	-OH	-H	-H
H126(a), (b), and (c)	S	-OH	-H	-Cl
H127(a), (b), and (c)	S	-OH	-H	-Br
H128(a), (b), and (c)	S	-OH	-H	-F
H129(a), (b), and (c)	S	-OH	-H	$-CH_3$
H130(a), (b), and (c)	S	-OH	-H	$-CF_3$
H131(a), (b), and (c)	S	-OH	-H	$-OCH_3$
H132(a), (b), and (c)	S	-OH	-H	$-OCH_2CH_3$
H133(a), (b), and (c)	S	-OH	-H	$-OCF_3$
H134(a), (b), and (c)	S	-OH	-H	-*tert*-butyl
H135(a), (b), and (c)	S	-OH	-H	-*iso*-propyl
H136(a), (b), and (c)	S	$-NO_2$	-Cl	-H
H137(a), (b), and (c)	S	$-NO_2$	-Br	-H
H138(a), (b), and (c)	S	$-NO_2$	-F	-H
H139(a), (b), and (c)	S	$-NO_2$	$-CH_3$	-H
H140(a), (b), and (c)	S	$-NO_2$	$-CF_3$	-H
H141(a), (b), and (c)	S	$-NO_2$	$-OCH_3$	-H
H142(a), (b), and (c)	S	$-NO_2$	$-OCH_2CH_3$	-H
H143(a), (b), and (c)	S	$-NO_2$	$-OCF_3$	-H
H144(a), (b), and (c)	S	$-NO_2$	-*tert*-butyl	-H
H145(a), (b), and (c)	S	$-NO_2$	-*iso*-propyl	-H
H146(a), (b), and (c)	S	$-NO_2$	$-CH_3$	$-CH_3$
H147(a), (b), and (c)	S	$-NO_2$	-H	-H
H148(a), (b), and (c)	S	$-NO_2$	-H	-Cl
H149(a), (b), and (c)	S	$-NO_2$	-H	-Br
H150(a), (b), and (c)	S	$-NO_2$	-H	-F
H151(a), (b), and (c)	S	$-NO_2$	-H	$-CH_3$
H152(a), (b), and (c)	S	$-NO_2$	-H	$-CF_3$
H153(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_3$
H154(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_2CH_3$
H155(a), (b), and (c)	S	$-NO_2$	-H	$-OCF_3$
H156(a), (b), and (c)	S	$-NO_2$	-H	-*tert*-butyl
H157(a), (b), and (c)	S	$-NO_2$	-H	-*iso*-propyl
H158(a), (b), and (c)	S	-CN	-Br	-H
H159(a), (b), and (c)	S	-CN	-Cl	-H
H160(a), (b), and (c)	S	-CN	-F	-H
H161(a), (b), and (c)	S	-CN	$-CH_3$	-H
H162(a), (b), and (c)	S	-CN	$-CF_3$	-H
H163(a), (b), and (c)	S	-CN	$-OCH_3$	-H
H164(a), (b), and (c)	S	-CN	$-OCH_2CH_3$	-H
H165(a), (b), and (c)	S	-CN	$-OCF_3$	-H
H166(a), (b), and (c)	S	-CN	-*tert*-butyl	-H
H167(a), (b), and (c)	S	-CN	-*iso*-propyl	-H
H168(a), (b), and (c)	S	-CN	$-CH_3$	$-CH_3$

H169(a), (b), and (c)	S	-CN	-H	-H
H170(a), (b), and (c)	S	-CN	-H	-Cl
H171(a), (b), and (c)	S	-CN	-H	-Br
H172(a), (b), and (c)	S	-CN	-H	-F
H173(a), (b), and (c)	S	-CN	-H	$-CH_3$
H174(a), (b), and (c)	S	-CN	-H	$-CF_3$
H175(a), (b), and (c)	S	-CN	-H	$-OCH_3$
H176(a), (b), and (c)	S	-CN	-H	$-OCH_2CH_3$
H177(a), (b), and (c)	S	-CN	-H	$-OCF_3$
H178(a), (b), and (c)	S	-CN	-H	-*tert*-butyl
H179(a), (b), and (c)	S	-CN	-H	-*iso*-propyl
H180(a), (b), and (c)	S	-Br	-Br	-H
H181(a), (b), and (c)	S	-Br	-Cl	-H
H182(a), (b), and (c)	S	-Br	-F	-H
H183(a), (b), and (c)	S	-Br	$-CH_3$	-H
H184(a), (b), and (c)	S	-Br	$-CF_3$	-H
H185(a), (b), and (c)	S	-Br	$-OCH_3$	-H
H186(a), (b), and (c)	S	-Br	$-OCH_2CH_3$	-H
H187(a), (b), and (c)	S	-Br	$-OCF_3$	-H
H188(a), (b), and (c)	S	-Br	-*tert*-butyl	-H
H189(a), (b), and (c)	S	-Br	-*iso*-propyl	-H
H190(a), (b), and (c)	S	-Br	$-CH_3$	$-CH_3$
H191(a), (b), and (c)	S	-Br	-H	-H
H192(a), (b), and (c)	S	-Br	-H	-Cl
H193(a), (b), and (c)	S	-Br	-H	-Br
H194(a), (b), and (c)	S	-Br	-H	-F
H195(a), (b), and (c)	S	-Br	-H	$-CH_3$
H196(a), (b), and (c)	S	-Br	-H	$-CF_3$
H197(a), (b), and (c)	S	-Br	-H	$-OCH_3$
H198(a), (b), and (c)	S	-Br	-H	$-OCH_2CH_3$
H199(a), (b), and (c)	S	-Br	-H	$-OCF_3$
H200(a), (b), and (c)	S	-Br	-H	-*tert*-butyl
H201(a), (b), and (c)	S	-Br	-H	-*iso*-propyl
H202(a), (b), and (c)	S	-I	-Cl	-H
H203(a), (b), and (c)	S	-I	-Br	-H
H204(a), (b), and (c)	S	-I	-F	-H
H205(a), (b), and (c)	S	-I	$-CH_3$	-H
H206(a), (b), and (c)	S	-I	$-CF_3$	-H
H207(a), (b), and (c)	S	-I	$-OCH_3$	-H
H208(a), (b), and (c)	S	-I	$-OCH_2CH_3$	-H
H209(a), (b), and (c)	S	-I	$-OCF_3$	-H
H210(a), (b), and (c)	S	-I	-*tert*-butyl	-H
H211(a), (b), and (c)	S	-I	-*iso*-propyl	-H
H212(a), (b), and (c)	S	-I	$-CH_3$	$-CH_3$
H213(a), (b), and (c)	S	-I	-H	-H
H214(a), (b), and (c)	S	-I	-H	-Cl
H215(a), (b), and (c)	S	-I	-H	-Br
H216(a), (b), and (c)	S	-I	-H	-F

H217(a), (b), and (c)	S	-I	-H	$-CH_3$
H218(a), (b), and (c)	S	-I	-H	$-CF_3$
H219(a), (b), and (c)	S	-I	-H	$-OCH_3$
H220(a), (b), and (c)	S	-I	-H	$-OCH_2CH_3$
H221(a), (b), and (c)	S	-I	-H	$-OCF_3$
H222(a), (b), and (c)	S	-I	-H	*-tert*-butyl
H223(a), (b), and (c)	S	-I	-H	*-iso*-propyl
H224(a), (b), and (c)	O	-H	-Cl	-H
H225(a), (b), and (c)	O	-H	-Br	-H
H226(a), (b), and (c)	O	-H	-F	-H
H227(a), (b), and (c)	O	-H	$-CH_3$	-H
H228(a), (b), and (c)	O	-H	$-CF_3$	-H
H229(a), (b), and (c)	O	-H	$-OCH_3$	-H
H230(a), (b), and (c)	O	-H	$-OCH_2CH_3$	-H
H231(a), (b), and (c)	O	-H	$-OCF_3$	-H
H232(a), (b), and (c)	O	-H	*-tert*-butyl	-H
H233(a), (b), and (c)	O	-H	*-iso*-propyl	-H
H234(a), (b), and (c)	O	-H	$-CH_3$	$-CH_3$
H235(a), (b), and (c)	O	-H	-H	-H
H236(a), (b), and (c)	O	-H	-H	-Cl
H237(a), (b), and (c)	O	-H	-H	-Br
H238(a), (b), and (c)	O	-H	-H	-F
H239(a), (b), and (c)	O	-H	-H	$-CH_3$
H240(a), (b), and (c)	O	-H	-H	$-CF_3$
H241(a), (b), and (c)	O	-H	-H	$-OCH_3$
H242(a), (b), and (c)	O	-H	-H	$-OCH_2CH_3$
H243(a), (b), and (c)	O	-H	-H	$-OCF_3$
H244(a), (b), and (c)	O	-H	-H	*-tert*-butyl
H245(a), (b), and (c)	O	-H	-H	*-iso*-propyl
H246(a), (b), and (c)	O	-Cl	-Cl	-H
H247(a), (b), and (c)	O	-Cl	-Br	-H
H248(a), (b), and (c)	O	-Cl	-F	-H
H249(a), (b), and (c)	O	-Cl	$-CH_3$	-H
H250(a), (b), and (c)	O	-Cl	$-CF_3$	-H
H251(a), (b), and (c)	O	-Cl	$-OCH_3$	-H
H252(a), (b), and (c)	O	-Cl	$-OCH_2CH_3$	-H
H253(a), (b), and (c)	O	-Cl	$-OCF_3$	-H
H254(a), (b), and (c)	O	-Cl	*-tert*-butyl	-H
H255(a), (b), and (c)	O	-Cl	*-iso*-propyl	-H
H256(a), (b), and (c)	O	-Cl	$-CH_3$	$-CH_3$
H257(a), (b), and (c)	O	-Cl	-H	-H
H258(a), (b), and (c)	O	-Cl	-H	$-CH_3$
H259(a), (b), and (c)	O	-Cl	-H	-Cl
H260(a), (b), and (c)	O	-Cl	-H	-Br
H261(a), (b), and (c)	O	-Cl	-H	-F
H262(a), (b), and (c)	O	-Cl	-H	$-CF_3$
H263(a), (b), and (c)	O	-Cl	-H	$-OCH_3$
H264(a), (b), and (c)	O	-Cl	-H	$-OCH_2CH_3$

H265(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
H266(a), (b), and (c)	O	-Cl	-H	*-tert*-butyl
H267(a), (b), and (c)	O	-Cl	-H	*-iso*-propyl
H268(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
H269(a), (b), and (c)	O	-Cl	-H	*-tert*-butyl
H270(a), (b), and (c)	O	-Cl	-H	*-iso*-propyl
H271(a), (b), and (c)	O	$-CH_3$	-Cl	-H
H272(a), (b), and (c)	O	$-CH_3$	-Br	-H
H273(a), (b), and (c)	O	$-CH_3$	-F	-H
H274(a), (b), and (c)	O	$-CH_3$	$-CH_3$	-H
H275(a), (b), and (c)	O	$-CH_3$	$-CF_3$	-H
H276(a), (b), and (c)	O	$-CH_3$	$-OCH_3$	-H
H277(a), (b), and (c)	O	$-CH_3$	$-OCH_2CH_3$	-H
H278(a), (b), and (c)	O	$-CH_3$	$-OCF_3$	-H
H279(a), (b), and (c)	O	$-CH_3$	*-tert*-butyl	-H
H280(a), (b), and (c)	O	$-CH_3$	*-iso*-propyl	-H
H281(a), (b), and (c)	O	$-CH_3$	$-CH_3$	$-CH_3$
H282(a), (b), and (c)	O	$-CH_3$	-H	-H
H283(a), (b), and (c)	O	$-CH_3$	-H	-Cl
H284(a), (b), and (c)	O	$-CH_3$	-H	-Br
H285(a), (b), and (c)	O	$-CH_3$	-H	-F
H286(a), (b), and (c)	O	$-CH_3$	-H	$-CH_3$
H287(a), (b), and (c)	O	$-CH_3$	-H	$-CF_3$
H288(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_3$
H289(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_2CH_3$
H290(a), (b), and (c)	O	$-CH_3$	-H	$-OCF_3$
H291(a), (b), and (c)	O	$-CH_3$	-H	*-tert*-butyl
H292(a), (b), and (c)	O	$-CH_3$	-H	*-iso*-propyl
H293(a), (b), and (c)	O	$-CF_3$	-Cl	-H
H294(a), (b), and (c)	O	$-CF_3$	-Br	-H
H295(a), (b), and (c)	O	$-CF_3$	-F	-H
H296(a), (b), and (c)	O	$-CF_3$	$-CH_3$	-H
H297(a), (b), and (c)	O	$-CF_3$	$-CF_3$	-H
H298(a), (b), and (c)	O	$-CF_3$	$-OCH_3$	-H
H299(a), (b), and (c)	O	$-CF_3$	$-OCH_2CH_3$	-H
H300(a), (b), and (c)	O	$-CF_3$	$-OCF_3$	-H
H301(a), (b), and (c)	O	$-CF_3$	*-tert*-butyl	-H
H302(a), (b), and (c)	O	$-CF_3$	*-iso*-propyl	-H
H303(a), (b), and (c)	O	$-CF_3$	$-CH_3$	$-CH_3$
H304(a), (b), and (c)	O	$-CF_3$	-H	-H
H305(a), (b), and (c)	O	$-CF_3$	-H	-Cl
H306(a), (b), and (c)	O	$-CF_3$	-H	-Br
H307(a), (b), and (c)	O	$-CF_3$	-H	-F
H308(a), (b), and (c)	O	$-CF_3$	-H	$-CH_3$
H309(a), (b), and (c)	O	$-CF_3$	-H	$-CF_3$
H310(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_3$
H311(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_2CH_3$
H312(a), (b), and (c)	O	$-CF_3$	-H	$-OCF_3$

H313(a), (b), and (c)	O	$-CF_3$	-H	-*tert*-butyl
H314(a), (b), and (c)	O	$-CF_3$	-H	-*iso*-propyl
H315(a), (b), and (c)	O	$-CHF_2$	-Cl	-H
H316(a), (b), and (c)	O	$-CHF_2$	-Br	-H
H317(a), (b), and (c)	O	$-CHF_2$	-F	-H
H318(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	-H
H319(a), (b), and (c)	O	$-CHF_2$	$-CF_3$	-H
H320(a), (b), and (c)	O	$-CHF_2$	$-OCH_3$	-H
H321(a), (b), and (c)	O	$-CHF_2$	$-OCH_2CH_3$	-H
H322(a), (b), and (c)	O	$-CHF_2$	$-OCF_3$	-H
H323(a), (b), and (c)	O	$-CHF_2$	-*tert*-butyl	-H
H324(a), (b), and (c)	O	$-CHF_2$	-*iso*-propyl	-H
H325(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	$-CH_3$
H326(a), (b), and (c)	O	$-CHF_2$	-H	-H
H327(a), (b), and (c)	O	$-CHF_2$	-H	-Cl
H328(a), (b), and (c)	O	$-CHF_2$	-H	-Br
H329(a), (b), and (c)	O	$-CHF_2$	-H	-F
H330(a), (b), and (c)	O	$-CHF_2$	-H	$-CH_3$
H331(a), (b), and (c)	O	$-CHF_2$	-H	$-CF_3$
H332(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_3$
H333(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_2CH_3$
H334(a), (b), and (c)	O	$-CHF_2$	-H	$-OCF_3$
H335(a), (b), and (c)	O	$-CHF_2$	-H	-*tert*-butyl
H336(a), (b), and (c)	O	$-CHF_2$	-H	-*iso*-propyl
H337(a), (b), and (c)	O	-OH	-Cl	-H
H338(a), (b), and (c)	O	-OH	-Br	-H
H339(a), (b), and (c)	O	-OH	-F	-H
H340(a), (b), and (c)	O	-OH	$-CH_3$	-H
H341(a), (b), and (c)	O	-OH	$-CF_3$	-H
H342(a), (b), and (c)	O	-OH	$-OCH_3$	-H
H343(a), (b), and (c)	O	-OH	$-OCH_2CH_3$	-H
H344(a), (b), and (c)	O	-OH	$-OCF_3$	-H
H345(a), (b), and (c)	O	-OH	-*tert*-butyl	-H
H346(a), (b), and (c)	O	-OH	-*iso*-propyl	-H
H347(a), (b), and (c)	O	-OH	$-CH_3$	$-CH_3$
H348(a), (b), and (c)	O	-OH	-H	-H
H349(a), (b), and (c)	O	-OH	-H	-Cl
H350(a), (b), and (c)	O	-OH	-H	-Br
H351(a), (b), and (c)	O	-OH	-H	-F
H352(a), (b), and (c)	O	-OH	-H	$-CH_3$
H353(a), (b), and (c)	O	-OH	-H	$-CF_3$
H354(a), (b), and (c)	O	-OH	-H	$-OCH_3$
H355(a), (b), and (c)	O	-OH	-H	$-OCH_2CH_3$
H356(a), (b), and (c)	O	-OH	-H	$-OCF_3$
H357(a), (b), and (c)	O	-OH	-H	-*tert*-butyl
H358(a), (b), and (c)	O	-OH	-H	-*iso*-propyl
H359(a), (b), and (c)	O	$-NO_2$	-Cl	-H
H360(a), (b), and (c)	O	$-NO_2$	-Br	-H

H361(a), (b), and (c)	O	$-NO_2$	-F	-H
H362(a), (b), and (c)	O	$-NO_2$	$-CH_3$	-H
H363(a), (b), and (c)	O	$-NO_2$	$-CF_3$	-H
H364(a), (b), and (c)	O	$-NO_2$	$-OCH_3$	-H
H365(a), (b), and (c)	O	$-NO_2$	$-OCH_2CH_3$	-H
H366(a), (b), and (c)	O	$-NO_2$	$-OCF_3$	-H
H367(a), (b), and (c)	O	$-NO_2$	*-tert*-butyl	-H
H368(a), (b), and (c)	O	$-NO_2$	*-iso*-propyl	-H
H369(a), (b), and (c)	O	$-NO_2$	$-CH_3$	$-CH_3$
H370(a), (b), and (c)	O	$-NO_2$	-H	-H
H371(a), (b), and (c)	O	$-NO_2$	-H	-Cl
H372(a), (b), and (c)	O	$-NO_2$	-H	-Br
H373(a), (b), and (c)	O	$-NO_2$	-H	-F
H374(a), (b), and (c)	O	$-NO_2$	-H	$-CH_3$
H375(a), (b), and (c)	O	$-NO_2$	-H	$-CF_3$
H376(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_3$
H377(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_2CH_3$
H378(a), (b), and (c)	O	$-NO_2$	-H	$-OCF_3$
H379(a), (b), and (c)	O	$-NO_2$	-H	*-tert*-butyl
H380(a), (b), and (c)	O	$-NO_2$	-H	*-iso*-propyl
H381(a), (b), and (c)	O	-CN	-Br	-H
H382(a), (b), and (c)	O	-CN	-Cl	-H
H383(a), (b), and (c)	O	-CN	-F	-H
H384(a), (b), and (c)	O	-CN	$-CH_3$	-H
H385(a), (b), and (c)	O	-CN	$-CF_3$	-H
H386(a), (b), and (c)	O	-CN	$-OCH_3$	-H
H387(a), (b), and (c)	O	-CN	$-OCH_2CH_3$	-H
H388(a), (b), and (c)	O	-CN	$-OCF_3$	-H
H389(a), (b), and (c)	O	-CN	*-tert*-butyl	-H
H390(a), (b), and (c)	O	-CN	*-iso*-propyl	-H
H391(a), (b), and (c)	O	-CN	$-CH_3$	$-CH_3$
H392(a), (b), and (c)	O	-CN	-H	-H
H393(a), (b), and (c)	O	-CN	-H	-Cl
H394(a), (b), and (c)	O	-CN	-H	-Br
H395(a), (b), and (c)	O	-CN	-H	-F
H396(a), (b), and (c)	O	-CN	-H	$-CH_3$
H397(a), (b), and (c)	O	-CN	-H	$-CF_3$
H398(a), (b), and (c)	O	-CN	-H	$-OCH_3$
H399(a), (b), and (c)	O	-CN	-H	$-OCH_2CH_3$
H400(a), (b), and (c)	O	-CN	-H	$-OCF_3$
H401(a), (b), and (c)	O	-CN	-H	*-tert*-butyl
H402(a), (b), and (c)	O	-CN	-H	*-iso*-propyl
H403(a), (b), and (c)	O	-Br	-Br	-H
H404(a), (b), and (c)	O	-Br	-Cl	-H
H405(a), (b), and (c)	O	-Br	-F	-H
H406(a), (b), and (c)	O	-Br	$-CH_3$	-H
H407(a), (b), and (c)	O	-Br	$-CF_3$	-H
H408(a), (b), and (c)	O	-Br	$-OCH_3$	-H

H409(a), (b), and (c)	O	-Br	$-OCH_2CH_3$	-H
H410(a), (b), and (c)	O	-Br	$-OCF_3$	-H
H411(a), (b), and (c)	O	-Br	*-tert*-butyl	-H
H412(a), (b), and (c)	O	-Br	*-iso*-propyl	-H
H413(a), (b), and (c)	O	-Br	$-CH_3$	$-CH_3$
H414(a), (b), and (c)	O	-Br	-H	-H
H415(a), (b), and (c)	O	-Br	-H	-Cl
H416(a), (b), and (c)	O	-Br	-H	-Br
H417(a), (b), and (c)	O	-Br	-H	-F
H418(a), (b), and (c)	O	-Br	-H	$-CH_3$
H419(a), (b), and (c)	O	-Br	-H	$-CF_3$
H420(a), (b), and (c)	O	-Br	-H	$-OCH_3$
H421(a), (b), and (c)	O	-Br	-H	$-OCH_2CH_3$
H422(a), (b), and (c)	O	-Br	-H	$-OCF_3$
H423(a), (b), and (c)	O	-Br	-H	*-tert*-butyl
H424(a), (b), and (c)	O	-Br	-H	*-iso*-propyl
H425(a), (b), and (c)	O	-I	-Cl	-H
H426(a), (b), and (c)	O	-I	-Br	-H
H427(a), (b), and (c)	O	-I	-F	-H
H428(a), (b), and (c)	O	-I	$-CH_3$	-H
H429(a), (b), and (c)	O	-I	$-CF_3$	-H
H430(a), (b), and (c)	O	-I	$-OCH_3$	-H
H431(a), (b), and (c)	O	-I	$-OCH_2CH_3$	-H
H432(a), (b), and (c)	O	-I	$-OCF_3$	-H
H433(a), (b), and (c)	O	-I	*-tert*-butyl	-H
H434(a), (b), and (c)	O	-I	*-iso*-propyl	-H
H435(a), (b), and (c)	O	-I	$-CH_3$	$-CH_3$
H436(a), (b), and (c)	O	-I	-H	-H
H437(a), (b), and (c)	O	-I	-H	-Cl
H438(a), (b), and (c)	O	-I	-H	-Br
H439(a), (b), and (c)	O	-I	-H	-F
H440(a), (b), and (c)	O	-I	-H	$-CH_3$
H441(a), (b), and (c)	O	-I	-H	$-CF_3$
H442(a), (b), and (c)	O	-I	-H	$-OCH_3$
H443(a), (b), and (c)	O	-I	-H	$-OCH_2CH_3$
H444(a), (b), and (c)	O	-I	-H	$-OCF_3$
H445(a), (b), and (c)	O	-I	-H	*-tert*-butyl
H446(a), (b), and (c)	O	-I	-H	*-iso*-propyl
H447(a), (b), and (c)	NH	-H	-Cl	-H
H448(a), (b), and (c)	NH	-H	-Br	-H
H449(a), (b), and (c)	NH	-H	-F	-H
H450(a), (b), and (c)	NH	-H	$-CH_3$	-H
H451(a), (b), and (c)	NH	-H	$-CF_3$	-H
H452(a), (b), and (c)	NH	-H	$-OCH_3$	-H
H453(a), (b), and (c)	NH	-H	$-OCH_2CH_3$	-H
H454(a), (b), and (c)	NH	-H	$-OCF_3$	-H
H455(a), (b), and (c)	NH	-H	*-tert*-butyl	-H
H456(a), (b), and (c)	NH	-H	*-iso*-propyl	-H

H457(a), (b), and (c)	NH	-H	$-CH_3$	$-CH_3$
H458(a), (b), and (c)	NH	-H	-H	-H
H459(a), (b), and (c)	NH	-H	-H	-Cl
H460(a), (b), and (c)	NH	-H	-H	-Br
H461(a), (b), and (c)	NH	-H	-H	-F
H462(a), (b), and (c)	NH	-H	-H	$-CH_3$
H463(a), (b), and (c)	NH	-H	-H	$-CF_3$
H464(a), (b), and (c)	NH	-H	-H	$-OCH_3$
H465(a), (b), and (c)	NH	-H	-H	$-OCH_2CH_3$
H466(a), (b), and (c)	NH	-H	-H	$-OCF_3$
H467(a), (b), and (c)	NH	-H	-H	-*tert*-butyl
H468(a), (b), and (c)	NH	-H	-H	-*iso*-propyl
H469(a), (b), and (c)	NH	-Cl	-Cl	-H
H470(a), (b), and (c)	NH	-Cl	-Br	-H
H471(a), (b), and (c)	NH	-Cl	-F	-H
H472(a), (b), and (c)	NH	-Cl	$-CH_3$	-H
H473(a), (b), and (c)	NH	-Cl	$-CF_3$	-H
H474(a), (b), and (c)	NH	-Cl	$-OCH_3$	-H
H475(a), (b), and (c)	NH	-Cl	$-OCH_2CH_3$	-H
H476(a), (b), and (c)	NH	-Cl	$-OCF_3$	-H
H477(a), (b), and (c)	NH	-Cl	-*tert*-butyl	-H
H478(a), (b), and (c)	NH	-Cl	-*iso*-propyl	-H
H479(a), (b), and (c)	NH	-Cl	$-CH_3$	$-CH_3$
H480(a), (b), and (c)	NH	-Cl	-H	-H
H481(a), (b), and (c)	NH	-Cl	-H	$-CH_3$
H482(a), (b), and (c)	NH	-Cl	-H	-Cl
H483(a), (b), and (c)	NH	-Cl	-H	-Br
H484(a), (b), and (c)	NH	-Cl	-H	-F
H485(a), (b), and (c)	NH	-Cl	-H	$-CF_3$
H486(a), (b), and (c)	NH	-Cl	-H	$-OCH_3$
H487(a), (b), and (c)	NH	-Cl	-H	$-OCH_2CH_3$
H488(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
H489(a), (b), and (c)	NH	-Cl	-H	-*tert*-butyl
H490(a), (b), and (c)	NH	-Cl	-H	-*iso*-propyl
H491(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
H492(a), (b), and (c)	NH	-Cl	-H	-*tert*-butyl
H493(a), (b), and (c)	NH	-Cl	-H	-*iso*-propyl
H494(a), (b), and (c)	NH	$-CH_3$	-Cl	-H
H495(a), (b), and (c)	NH	$-CH_3$	-Br	-H
H496(a), (b), and (c)	NH	$-CH_3$	-F	-H
H497(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	-H
H498(a), (b), and (c)	NH	$-CH_3$	$-CF_3$	-H
H499(a), (b), and (c)	NH	$-CH_3$	$-OCH_3$	-H
H500(a), (b), and (c)	NH	$-CH_3$	$-OCH_2CH_3$	-H
H501(a), (b), and (c)	NH	$-CH_3$	$-OCF_3$	-H
H502(a), (b), and (c)	NH	$-CH_3$	-*tert*-butyl	-H
H503(a), (b), and (c)	NH	$-CH_3$	-*iso*-propyl	-H
H504(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	$-CH_3$

H505(a), (b), and (c)	NH	$-CH_3$	-H	-H
H506(a), (b), and (c)	NH	$-CH_3$	-H	-Cl
H507(a), (b), and (c)	NH	$-CH_3$	-H	-Br
H508(a), (b), and (c)	NH	$-CH_3$	-H	-F
H509(a), (b), and (c)	NH	$-CH_3$	-H	$-CH_3$
H510(a), (b), and (c)	NH	$-CH_3$	-H	$-CF_3$
H511(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_3$
H512(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_2CH_3$
H513(a), (b), and (c)	NH	$-CH_3$	-H	$-OCF_3$
H514(a), (b), and (c)	NH	$-CH_3$	-H	*-tert*-butyl
H515(a), (b), and (c)	NH	$-CH_3$	-H	*-iso*-propyl
H516(a), (b), and (c)	NH	$-CF_3$	-Cl	-H
H517(a), (b), and (c)	NH	$-CF_3$	-Br	-H
H518(a), (b), and (c)	NH	$-CF_3$	-F	-H
H519(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	-H
H520(a), (b), and (c)	NH	$-CF_3$	$-CF_3$	-H
H521(a), (b), and (c)	NH	$-CF_3$	$-OCH_3$	-H
H522(a), (b), and (c)	NH	$-CF_3$	$-OCH_2CH_3$	-H
H523(a), (b), and (c)	NH	$-CF_3$	$-OCF_3$	-H
H524(a), (b), and (c)	NH	$-CF_3$	*-tert*-butyl	-H
H525(a), (b), and (c)	NH	$-CF_3$	*-iso*-propyl	-H
H526(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	$-CH_3$
H527(a), (b), and (c)	NH	$-CF_3$	-H	-H
H528(a), (b), and (c)	NH	$-CF_3$	-H	-Cl
H529(a), (b), and (c)	NH	$-CF_3$	-H	-Br
H530(a), (b), and (c)	NH	$-CF_3$	-H	-F
H531(a), (b), and (c)	NH	$-CF_3$	-H	$-CH_3$
H532(a), (b), and (c)	NH	$-CF_3$	-H	$-CF_3$
H533(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_3$
H534(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_2CH_3$
H535(a), (b), and (c)	NH	$-CF_3$	-H	$-OCF_3$
H536(a), (b), and (c)	NH	$-CF_3$	-H	*-tert*-butyl
H537(a), (b), and (c)	NH	$-CF_3$	-H	*-iso*-propyl
H538(a), (b), and (c)	NH	$-CHF_2$	-Cl	-H
H539(a), (b), and (c)	NH	$-CHF_2$	-Br	-H
H540(a), (b), and (c)	NH	$-CHF_2$	-F	-H
H541(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	-H
H542(a), (b), and (c)	NH	$-CHF_2$	$-CF_3$	-H
H543(a), (b), and (c)	NH	$-CHF_2$	$-OCH_3$	-H
H544(a), (b), and (c)	NH	$-CHF_2$	$-OCH_2CH_3$	-H
H545(a), (b), and (c)	NH	$-CHF_2$	$-OCF_3$	-H
H546(a), (b), and (c)	NH	$-CHF_2$	*-tert*-butyl	-H
H547(a), (b), and (c)	NH	$-CHF_2$	*-iso*-propyl	-H
H548(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	$-CH_3$
H549(a), (b), and (c)	NH	$-CHF_2$	-H	-H
H550(a), (b), and (c)	NH	$-CHF_2$	-H	-Cl
H551(a), (b), and (c)	NH	$-CHF_2$	-H	-Br
H552(a), (b), and (c)	NH	$-CHF_2$	-H	-F

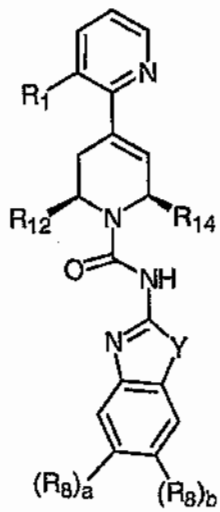
H553(a), (b), and (c)	NH	$-CHF_2$	-H	$-CH_3$
H554(a), (b), and (c)	NH	$-CHF_2$	-H	$-CF_3$
H555(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_3$
H556(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_2CH_3$
H557(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCF_3$
H558(a), (b), and (c)	NH	$-CHF_2$	-H	*-tert*-butyl
H559(a), (b), and (c)	NH	$-CHF_2$	-H	*-iso*-propyl
H560(a), (b), and (c)	NH	-OH	-Cl	-H
H561(a), (b), and (c)	NH	-OH	-Br	-H
H562(a), (b), and (c)	NH	-OH	-F	-H
H563(a), (b), and (c)	NH	-OH	$-CH_3$	-H
H564(a), (b), and (c)	NH	-OH	$-CF_3$	-H
H565(a), (b), and (c)	NH	-OH	$-OCH_3$	-H
H566(a), (b), and (c)	NH	-OH	$-OCH_2CH_3$	-H
H567(a), (b), and (c)	NH	-OH	$-OCF_3$	-H
H568(a), (b), and (c)	NH	-OH	*-tert*-butyl	-H
H569(a), (b), and (c)	NH	-OH	*-iso*-propyl	-H
H570(a), (b), and (c)	NH	-OH	$-CH_3$	$-CH_3$
H571(a), (b), and (c)	NH	-OH	-H	-H
H572(a), (b), and (c)	NH	-OH	-H	-Cl
H573(a), (b), and (c)	NH	-OH	-H	-Br
H574(a), (b), and (c)	NH	-OH	-H	-F
H575(a), (b), and (c)	NH	-OH	-H	$-CH_3$
H576(a), (b), and (c)	NH	-OH	-H	$-CF_3$
H577(a), (b), and (c)	NH	-OH	-H	$-OCH_3$
H578(a), (b), and (c)	NH	-OH	-H	$-OCH_2CH_3$
H579(a), (b), and (c)	NH	-OH	-H	$-OCF_3$
H580(a), (b), and (c)	NH	-OH	-H	*-tert*-butyl
H581(a), (b), and (c)	NH	-OH	-H	*-iso*-propyl
H582(a), (b), and (c)	NH	$-NO_2$	-Cl	-H
H583(a), (b), and (c)	NH	$-NO_2$	-Br	-H
H584(a), (b), and (c)	NH	$-NO_2$	-F	-H
H585(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	-H
H586(a), (b), and (c)	NH	$-NO_2$	$-CF_3$	-H
H587(a), (b), and (c)	NH	$-NO_2$	$-OCH_3$	-H
H588(a), (b), and (c)	NH	$-NO_2$	$-OCH_2CH_3$	-H
H589(a), (b), and (c)	NH	$-NO_2$	$-OCF_3$	-H
H590(a), (b), and (c)	NH	$-NO_2$	*-tert*-butyl	-H
H591(a), (b), and (c)	NH	$-NO_2$	*-iso*-propyl	-H
H592(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	$-CH_3$
H593(a), (b), and (c)	NH	$-NO_2$	-H	-H
H594(a), (b), and (c)	NH	$-NO_2$	-H	-Cl
H595(a), (b), and (c)	NH	$-NO_2$	-H	-Br
H596(a), (b), and (c)	NH	$-NO_2$	-H	-F
H597(a), (b), and (c)	NH	$-NO_2$	-H	$-CH_3$
H598(a), (b), and (c)	NH	$-NO_2$	-H	$-CF_3$
H599(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_3$
H600(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_2CH_3$

H601(a), (b), and (c)	NH	$-NO_2$	-H	$-OCF_3$
H602(a), (b), and (c)	NH	$-NO_2$	-H	*-tert*-butyl
H603(a), (b), and (c)	NH	$-NO_2$	-H	*-iso*-propyl
H604(a), (b), and (c)	NH	-CN	-Br	-H
H605(a), (b), and (c)	NH	-CN	-Cl	-H
H606(a), (b), and (c)	NH	-CN	-F	-H
H607(a), (b), and (c)	NH	-CN	$-CH_3$	-H
H608(a), (b), and (c)	NH	-CN	$-CF_3$	-H
H609(a), (b), and (c)	NH	-CN	$-OCH_3$	-H
H610(a), (b), and (c)	NH	-CN	$-OCH_2CH_3$	-H
H611(a), (b), and (c)	NH	-CN	$-OCF_3$	-H
H612(a), (b), and (c)	NH	-CN	*-tert*-butyl	-H
H613(a), (b), and (c)	NH	-CN	*-iso*-propyl	-H
H614(a), (b), and (c)	NH	-CN	$-CH_3$	$-CH_3$
H615(a), (b), and (c)	NH	-CN	-H	-H
H616(a), (b), and (c)	NH	-CN	-H	-Cl
H617(a), (b), and (c)	NH	-CN	-H	-Br
H618(a), (b), and (c)	NH	-CN	-H	-F
H619(a), (b), and (c)	NH	-CN	-H	$-CH_3$
H620(a), (b), and (c)	NH	-CN	-H	$-CF_3$
H621(a), (b), and (c)	NH	-CN	-H	$-OCH_3$
H622(a), (b), and (c)	NH	-CN	-H	$-OCH_2CH_3$
H623(a), (b), and (c)	NH	-CN	-H	$-OCF_3$
H624(a), (b), and (c)	NH	-CN	-H	*-tert*-butyl
H625(a), (b), and (c)	NH	-CN	-H	*-iso*-propyl
H626(a), (b), and (c)	NH	-Br	-Br	-H
H627(a), (b), and (c)	NH	-Br	-Cl	-H
H628(a), (b), and (c)	NH	-Br	-F	-H
H629(a), (b), and (c)	NH	-Br	$-CH_3$	-H
H630(a), (b), and (c)	NH	-Br	$-CF_3$	-H
H631(a), (b), and (c)	NH	-Br	$-OCH_3$	-H
H632(a), (b), and (c)	NH	-Br	$-OCH_2CH_3$	-H
H633(a), (b), and (c)	NH	-Br	$-OCF_3$	-H
H634(a), (b), and (c)	NH	-Br	*-tert*-butyl	-H
H635(a), (b), and (c)	NH	-Br	*-iso*-propyl	-H
H636(a), (b), and (c)	NH	-Br	$-CH_3$	$-CH_3$
H637(a), (b), and (c)	NH	-Br	-H	-H
H638(a), (b), and (c)	NH	-Br	-H	-Cl
H639(a), (b), and (c)	NH	-Br	-H	-Br
H640(a), (b), and (c)	NH	-Br	-H	-F
H641(a), (b), and (c)	NH	-Br	-H	$-CH_3$
H642(a), (b), and (c)	NH	-Br	-H	$-CF_3$
H643(a), (b), and (c)	NH	-Br	-H	$-OCH_3$
H644(a), (b), and (c)	NH	-Br	-H	$-OCH_2CH_3$
H645(a), (b), and (c)	NH	-Br	-H	$-OCF_3$
H646(a), (b), and (c)	NH	-Br	-H	*-tert*-butyl
H647(a), (b), and (c)	NH	-Br	-H	*-iso*-propyl
H648(a), (b), and (c)	NH	-I	-Cl	-H

H649(a), (b), and (c)	NH	-I	-Br	-H
H650(a), (b), and (c)	NH	-I	-F	-H
H651(a), (b), and (c)	NH	-I	$-CH_3$	-H
H652(a), (b), and (c)	NH	-I	$-CF_3$	-H
H653(a), (b), and (c)	NH	-I	$-OCH_3$	-H
H654(a), (b), and (c)	NH	-I	$-OCH_2CH_3$	-H
H655(a), (b), and (c)	NH	-I	$-OCF_3$	-H
H656(a), (b), and (c)	NH	-I	*-tert*-butyl	-H
H657(a), (b), and (c)	NH	-I	*-iso*-propyl	-H
H658(a), (b), and (c)	NH	-I	$-CH_3$	$-CH_3$
H659(a), (b), and (c)	NH	-I	-H	-H
H660(a), (b), and (c)	NH	-I	-H	-Cl
H661(a), (b), and (c)	NH	-I	-H	-Br
H662(a), (b), and (c)	NH	-I	-H	-F
H663(a), (b), and (c)	NH	-I	-H	$-CH_3$
H664(a), (b), and (c)	NH	-I	-H	$-CF_3$
H665(a), (b), and (c)	NH	-I	-H	$-OCH_3$
H666(a), (b), and (c)	NH	-I	-H	$-OCH_2CH_3$
H667(a), (b), and (c)	NH	-I	-H	$-OCF_3$
H668(a), (b), and (c)	NH	-I	-H	*-tert*-butyl
H669(a), (b), and (c)	NH	-I	-H	*-iso*-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 9



(IIa)

and pharmaceutically acceptable salts thereof, where:

Compound	Y	R_1	$(R_8)_a$	$(R_8)_b$
I01(a), (b), and (c)	S	-Cl	-Cl	-H
I02(a), (b), and (c)	S	-Cl	-Br	-H
I03(a), (b), and (c)	S	-Cl	-F	-H
I04(a), (b), and (c)	S	-Cl	$-CH_3$	-H
I05(a), (b), and (c)	S	-Cl	$-CF_3$	-H
I06(a), (b), and (c)	S	-Cl	$-OCH_3$	-H
I07(a), (b), and (c)	S	-Cl	$-OCH_2CH_3$	-H
I08(a), (b), and (c)	S	-Cl	$-OCF_3$	-H
I09(a), (b), and (c)	S	-Cl	-*tert*-butyl	-H
I10(a), (b), and (c)	S	-Cl	-*iso*-propyl	-H
I11(a), (b), and (c)	S	-Cl	$-CH_3$	$-CH_3$
I12(a), (b), and (c)	S	-Cl	-H	-H
I13(a), (b), and (c)	S	-Cl	-H	-Cl
I14(a), (b), and (c)	S	-Cl	-H	-Br
I15(a), (b), and (c)	S	-Cl	-H	-F
I16(a), (b), and (c)	S	-Cl	-H	$-CH_3$
I17(a), (b), and (c)	S	-Cl	-H	$-CF_3$
I18(a), (b), and (c)	S	-Cl	-H	$-OCH_3$
I19(a), (b), and (c)	S	-Cl	-H	$-OCH_2CH_3$
I20(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
I21(a), (b), and (c)	S	-Cl	-H	-*tert*-butyl
I22(a), (b), and (c)	S	-Cl	-H	-*iso*-propyl
I23(a), (b), and (c)	S	-Cl	-H	$-OCF_3$
I24(a), (b), and (c)	S	-Cl	-H	-*tert*-butyl
I25(a), (b), and (c)	S	-Cl	-H	-*iso*-propyl

I26(a), (b), and (c)	S	$-CH_3$	-Cl	-H
I27(a), (b), and (c)	S	$-CH_3$	-Br	-H
I28(a), (b), and (c)	S	$-CH_3$	-F	-H
I29(a), (b), and (c)	S	$-CH_3$	$-CH_3$	-H
I30(a), (b), and (c)	S	$-CH_3$	$-CF_3$	-H
I31(a), (b), and (c)	S	$-CH_3$	$-OCH_3$	-H
I32(a), (b), and (c)	S	$-CH_3$	$-OCH_2CH_3$	-H
I33(a), (b), and (c)	S	$-CH_3$	$-OCF_3$	-H
I34(a), (b), and (c)	S	$-CH_3$	*-tert*-butyl	-H
I35(a), (b), and (c)	S	$-CH_3$	*-iso*-propyl	-H
I36(a), (b), and (c)	S	$-CH_3$	$-CH_3$	$-CH_3$
I37(a), (b), and (c)	S	$-CH_3$	-H	-H
I38(a), (b), and (c)	S	$-CH_3$	-H	-Cl
I39(a), (b), and (c)	S	$-CH_3$	-H	-Br
I40(a), (b), and (c)	S	$-CH_3$	-H	-F
I41(a), (b), and (c)	S	$-CH_3$	-H	$-CH_3$
I42(a), (b), and (c)	S	$-CH_3$	-H	$-CF_3$
I43(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_3$
I44(a), (b), and (c)	S	$-CH_3$	-H	$-OCH_2CH_3$
I45(a), (b), and (c)	S	$-CH_3$	-H	$-OCF_3$
I46(a), (b), and (c)	S	$-CH_3$	-H	*-tert*-butyl
I47(a), (b), and (c)	S	$-CH_3$	-H	*-iso*-propyl
I48(a), (b), and (c)	S	$-CF_3$	-Cl	-H
I49(a), (b), and (c)	S	$-CF_3$	-Br	-H
I50(a), (b), and (c)	S	$-CF_3$	-F	-H
I51(a), (b), and (c)	S	$-CF_3$	$-CH_3$	-H
I52(a), (b), and (c)	S	$-CF_3$	$-CF_3$	-H
I53(a), (b), and (c)	S	$-CF_3$	$-OCH_3$	-H
I54(a), (b), and (c)	S	$-CF_3$	$-OCH_2CH_3$	-H
I55(a), (b), and (c)	S	$-CF_3$	$-OCF_3$	-H
I56(a), (b), and (c)	S	$-CF_3$	*-tert*-butyl	-H
I57(a), (b), and (c)	S	$-CF_3$	*-iso*-propyl	-H
I58(a), (b), and (c)	S	$-CF_3$	$-CH_3$	$-CH_3$
I59(a), (b), and (c)	S	$-CF_3$	-H	-H
I60(a), (b), and (c)	S	$-CF_3$	-H	-Cl
I61(a), (b), and (c)	S	$-CF_3$	-H	-Br
I62(a), (b), and (c)	S	$-CF_3$	-H	-F
I63(a), (b), and (c)	S	$-CF_3$	-H	$-CH_3$
I64(a), (b), and (c)	S	$-CF_3$	-H	$-CF_3$
I65(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_3$
I66(a), (b), and (c)	S	$-CF_3$	-H	$-OCH_2CH_3$
I67(a), (b), and (c)	S	$-CF_3$	-H	$-OCF_3$
I68(a), (b), and (c)	S	$-CF_3$	-H	*-tert*-butyl
I69(a), (b), and (c)	S	$-CF_3$	-H	*-iso*-propyl
I70(a), (b), and (c)	S	$-CHF_2$	-Cl	-H
I71(a), (b), and (c)	S	$-CHF_2$	-Br	-H
I72(a), (b), and (c)	S	$-CHF_2$	-F	-H
I73(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	-H

I74(a), (b), and (c)	S	$-CHF_2$	$-CF_3$	-H
I75(a), (b), and (c)	S	$-CHF_2$	$-OCH_3$	-H
I76(a), (b), and (c)	S	$-CHF_2$	$-OCH_2CH_3$	-H
I77(a), (b), and (c)	S	$-CHF_2$	$-OCF_3$	-H
I78(a), (b), and (c)	S	$-CHF_2$	*-tert*-butyl	-H
I79(a), (b), and (c)	S	$-CHF_2$	*-iso*-propyl	-H
I80(a), (b), and (c)	S	$-CHF_2$	$-CH_3$	$-CH_3$
I81(a), (b), and (c)	S	$-CHF_2$	-H	-H
I82(a), (b), and (c)	S	$-CHF_2$	-H	-Cl
I83(a), (b), and (c)	S	$-CHF_2$	-H	-Br
I84(a), (b), and (c)	S	$-CHF_2$	-H	-F
I85(a), (b), and (c)	S	$-CHF_2$	-H	$-CH_3$
I86(a), (b), and (c)	S	$-CHF_2$	-H	$-CF_3$
I87(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_3$
I88(a), (b), and (c)	S	$-CHF_2$	-H	$-OCH_2CH_3$
I89(a), (b), and (c)	S	$-CHF_2$	-H	$-OCF_3$
I90(a), (b), and (c)	S	$-CHF_2$	-H	*-tert*-butyl
I91(a), (b), and (c)	S	$-CHF_2$	-H	*-iso*-propyl
I92(a), (b), and (c)	S	-OH	-Cl	-H
I93(a), (b), and (c)	S	-OH	-Br	-H
I94(a), (b), and (c)	S	-OH	-F	-H
I95(a), (b), and (c)	S	-OH	$-CH_3$	-H
I96(a), (b), and (c)	S	-OH	$-CF_3$	-H
I97(a), (b), and (c)	S	-OH	$-OCH_3$	-H
I98(a), (b), and (c)	S	-OH	$-OCH_2CH_3$	-H
I99(a), (b), and (c)	S	-OH	$-OCF_3$	-H
I100(a), (b), and (c)	S	-OH	*-tert*-butyl	-H
I101(a), (b), and (c)	S	-OH	*-iso*-propyl	-H
I102(a), (b), and (c)	S	-OH	$-CH_3$	$-CH_3$
I103(a), (b), and (c)	S	-OH	-H	-H
I104(a), (b), and (c)	S	-OH	-H	-Cl
I105(a), (b), and (c)	S	-OH	-H	-Br
I106(a), (b), and (c)	S	-OH	-H	-F
I107(a), (b), and (c)	S	-OH	-H	$-CH_3$
I108(a), (b), and (c)	S	-OH	-H	$-CF_3$
I109(a), (b), and (c)	S	-OH	-H	$-OCH_3$
I110(a), (b), and (c)	S	-OH	-H	$-OCH_2CH_3$
I111(a), (b), and (c)	S	-OH	-H	$-OCF_3$
I112(a), (b), and (c)	S	-OH	-H	*-tert*-butyl
I113(a), (b), and (c)	S	-OH	-H	*-iso*-propyl
I114(a), (b), and (c)	S	$-NO_2$	-Cl	-H
I115(a), (b), and (c)	S	$-NO_2$	-Br	-H
I116(a), (b), and (c)	S	$-NO_2$	-F	-H
I117(a), (b), and (c)	S	$-NO_2$	$-CH_3$	-H
I118(a), (b), and (c)	S	$-NO_2$	$-CF_3$	-H
I119(a), (b), and (c)	S	$-NO_2$	$-OCH_3$	-H
I120(a), (b), and (c)	S	$-NO_2$	$-OCH_2CH_3$	-H
I121(a), (b), and (c)	S	$-NO_2$	$-OCF_3$	-H

I122(a), (b), and (c)	S	$-NO_2$	*-tert*-butyl	-H
I123(a), (b), and (c)	S	$-NO_2$	*-iso*-propyl	-H
I124(a), (b), and (c)	S	$-NO_2$	$-CH_3$	$-CH_3$
I125(a), (b), and (c)	S	$-NO_2$	-H	-H
I126(a), (b), and (c)	S	$-NO_2$	-H	-Cl
I127(a), (b), and (c)	S	$-NO_2$	-H	-Br
I128(a), (b), and (c)	S	$-NO_2$	-H	-F
I129(a), (b), and (c)	S	$-NO_2$	-H	$-CH_3$
I130(a), (b), and (c)	S	$-NO_2$	-H	$-CF_3$
I131(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_3$
I132(a), (b), and (c)	S	$-NO_2$	-H	$-OCH_2CH_3$
I133(a), (b), and (c)	S	$-NO_2$	-H	$-OCF_3$
I134(a), (b), and (c)	S	$-NO_2$	-H	*-tert*-butyl
I135(a), (b), and (c)	S	$-NO_2$	-H	*-iso*-propyl
I136(a), (b), and (c)	S	-CN	-Br	-H
I137(a), (b), and (c)	S	-CN	-Cl	-H
I138(a), (b), and (c)	S	-CN	-F	-H
I139(a), (b), and (c)	S	-CN	$-CH_3$	-H
I140(a), (b), and (c)	S	-CN	$-CF_3$	-H
I141(a), (b), and (c)	S	-CN	$-OCH_3$	-H
I142(a), (b), and (c)	S	-CN	$-OCH_2CH_3$	-H
I143(a), (b), and (c)	S	-CN	$-OCF_3$	-H
I144(a), (b), and (c)	S	-CN	*-tert*-butyl	-H
I145(a), (b), and (c)	S	-CN	*-iso*-propyl	-H
I146(a), (b), and (c)	S	-CN	$-CH_3$	$-CH_3$
I147(a), (b), and (c)	S	-CN	-H	-H
I148(a), (b), and (c)	S	-CN	-H	-Cl
I149(a), (b), and (c)	S	-CN	-H	-Br
I150(a), (b), and (c)	S	-CN	-H	-F
I151(a), (b), and (c)	S	-CN	-H	$-CH_3$
I152(a), (b), and (c)	S	-CN	-H	$-CF_3$
I153(a), (b), and (c)	S	-CN	-H	$-OCH_3$
I154(a), (b), and (c)	S	-CN	-H	$-OCH_2CH_3$
I155(a), (b), and (c)	S	-CN	-H	$-OCF_3$
I156(a), (b), and (c)	S	-CN	-H	*-tert*-butyl
I157(a), (b), and (c)	S	-CN	-H	*-iso*-propyl
I158(a), (b), and (c)	S	-Br	-Br	-H
I159(a), (b), and (c)	S	-Br	-Cl	-H
I160(a), (b), and (c)	S	-Br	-F	-H
I161(a), (b), and (c)	S	-Br	$-CH_3$	-H
I162(a), (b), and (c)	S	-Br	$-CF_3$	-H
I163(a), (b), and (c)	S	-Br	$-OCH_3$	-H
I164(a), (b), and (c)	S	-Br	$-OCH_2CH_3$	-H
I165(a), (b), and (c)	S	-Br	$-OCF_3$	-H
I166(a), (b), and (c)	S	-Br	*-tert*-butyl	-H
I167(a), (b), and (c)	S	-Br	*-iso*-propyl	-H
I168(a), (b), and (c)	S	-Br	$-CH_3$	$-CH_3$
I169(a), (b), and (c)	S	-Br	-H	-H

I170(a), (b), and (c)	S	-Br	-H	-Cl
I171(a), (b), and (c)	S	-Br	-H	-Br
I172(a), (b), and (c)	S	-Br	-H	-F
I173(a), (b), and (c)	S	-Br	-H	$-CH_3$
I174(a), (b), and (c)	S	-Br	-H	$-CF_3$
I175(a), (b), and (c)	S	-Br	-H	$-OCH_3$
I176(a), (b), and (c)	S	-Br	-H	$-OCH_2CH_3$
I177(a), (b), and (c)	S	-Br	-H	$-OCF_3$
I178(a), (b), and (c)	S	-Br	-H	*-tert*-butyl
I179(a), (b), and (c)	S	-Br	-H	*-iso*-propyl
I180(a), (b), and (c)	S	-I	-Cl	-H
I181(a), (b), and (c)	S	-I	-Br	-H
I182(a), (b), and (c)	S	-I	-F	-H
I183(a), (b), and (c)	S	-I	$-CH_3$	-H
I184(a), (b), and (c)	S	-I	$-CF_3$	-H
I185(a), (b), and (c)	S	-I	$-OCH_3$	-H
I186(a), (b), and (c)	S	-I	$-OCH_2CH_3$	-H
I187(a), (b), and (c)	S	-I	$-OCF_3$	-H
I188(a), (b), and (c)	S	-I	*-tert*-butyl	-H
I189(a), (b), and (c)	S	-I	*-iso*-propyl	-H
I190(a), (b), and (c)	S	-I	$-CH_3$	$-CH_3$
I191(a), (b), and (c)	S	-I	-H	-H
I192(a), (b), and (c)	S	-I	-H	-Cl
I193(a), (b), and (c)	S	-I	-H	-Br
I194(a), (b), and (c)	S	-I	-H	-F
I195(a), (b), and (c)	S	-I	-H	$-CH_3$
I196(a), (b), and (c)	S	-I	-H	$-CF_3$
I197(a), (b), and (c)	S	-I	-H	$-OCH_3$
I198(a), (b), and (c)	S	-I	-H	$-OCH_2CH_3$
I199(a), (b), and (c)	S	-I	-H	$-OCF_3$
I200(a), (b), and (c)	S	-I	-H	*-tert*-butyl
I201(a), (b), and (c)	S	-I	-H	*-iso*-propyl
I202(a), (b), and (c)	O	-Cl	-Cl	-H
I203(a), (b), and (c)	O	-Cl	-Br	-H
I204(a), (b), and (c)	O	-Cl	-F	-H
I205(a), (b), and (c)	O	-Cl	$-CH_3$	-H
I206(a), (b), and (c)	O	-Cl	$-CF_3$	-H
I207(a), (b), and (c)	O	-Cl	$-OCH_3$	-H
I208(a), (b), and (c)	O	-Cl	$-OCH_2CH_3$	-H
I209(a), (b), and (c)	O	-Cl	$-OCF_3$	-H
I210(a), (b), and (c)	O	-Cl	*-tert*-butyl	-H
I211(a), (b), and (c)	O	-Cl	*-iso*-propyl	-H
I212(a), (b), and (c)	O	-Cl	$-CH_3$	$-CH_3$
I213(a), (b), and (c)	O	-Cl	-H	-H
I214(a), (b), and (c)	O	-Cl	-H	$-CH_3$
I215(a), (b), and (c)	O	-Cl	-H	-Cl
I216(a), (b), and (c)	O	-Cl	-H	-Br
I217(a), (b), and (c)	O	-Cl	-H	-F

I218(a), (b), and (c)	O	-Cl	-H	$-CF_3$
I219(a), (b), and (c)	O	-Cl	-H	$-OCH_3$
I220(a), (b), and (c)	O	-Cl	-H	$-OCH_2CH_3$
I221(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
I222(a), (b), and (c)	O	-Cl	-H	*-tert*-butyl
I223(a), (b), and (c)	O	-Cl	-H	*-iso*-propyl
I224(a), (b), and (c)	O	-Cl	-H	$-OCF_3$
I225(a), (b), and (c)	O	-Cl	-H	*-tert*-butyl
I226(a), (b), and (c)	O	-Cl	-H	*-iso*-propyl
I227(a), (b), and (c)	O	$-CH_3$	-Cl	-H
I228(a), (b), and (c)	O	$-CH_3$	-Br	-H
I229(a), (b), and (c)	O	$-CH_3$	-F	-H
I230(a), (b), and (c)	O	$-CH_3$	$-CH_3$	-H
I231(a), (b), and (c)	O	$-CH_3$	$-CF_3$	-H
I232(a), (b), and (c)	O	$-CH_3$	$-OCH_3$	-H
I233(a), (b), and (c)	O	$-CH_3$	$-OCH_2CH_3$	-H
I234(a), (b), and (c)	O	$-CH_3$	$-OCF_3$	-H
I235(a), (b), and (c)	O	$-CH_3$	*-tert*-butyl	-H
I236(a), (b), and (c)	O	$-CH_3$	*-iso*-propyl	-H
I237(a), (b), and (c)	O	$-CH_3$	$-CH_3$	$-CH_3$
I238(a), (b), and (c)	O	$-CH_3$	-H	-H
I239(a), (b), and (c)	O	$-CH_3$	-H	-Cl
I240(a), (b), and (c)	O	$-CH_3$	-H	-Br
I241(a), (b), and (c)	O	$-CH_3$	-H	-F
I242(a), (b), and (c)	O	$-CH_3$	-H	$-CH_3$
I243(a), (b), and (c)	O	$-CH_3$	-H	$-CF_3$
I244(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_3$
I245(a), (b), and (c)	O	$-CH_3$	-H	$-OCH_2CH_3$
I246(a), (b), and (c)	O	$-CH_3$	-H	$-OCF_3$
I247(a), (b), and (c)	O	$-CH_3$	-H	*-tert*-butyl
I248(a), (b), and (c)	O	$-CH_3$	-H	*-iso*-propyl
I249(a), (b), and (c)	O	$-CF_3$	-Cl	-H
I250(a), (b), and (c)	O	$-CF_3$	-Br	-H
I251(a), (b), and (c)	O	$-CF_3$	-F	-H
I252(a), (b), and (c)	O	$-CF_3$	$-CH_3$	-H
I253(a), (b), and (c)	O	$-CF_3$	$-CF_3$	-H
I254(a), (b), and (c)	O	$-CF_3$	$-OCH_3$	-H
I255(a), (b), and (c)	O	$-CF_3$	$-OCH_2CH_3$	-H
I256(a), (b), and (c)	O	$-CF_3$	$-OCF_3$	-H
I257(a), (b), and (c)	O	$-CF_3$	*-tert*-butyl	-H
I258(a), (b), and (c)	O	$-CF_3$	*-iso*-propyl	-H
I259(a), (b), and (c)	O	$-CF_3$	$-CH_3$	$-CH_3$
I260(a), (b), and (c)	O	$-CF_3$	-H	-H
I261(a), (b), and (c)	O	$-CF_3$	-H	-Cl
I262(a), (b), and (c)	O	$-CF_3$	-H	-Br
I263(a), (b), and (c)	O	$-CF_3$	-H	-F
I264(a), (b), and (c)	O	$-CF_3$	-H	$-CH_3$
I265(a), (b), and (c)	O	$-CF_3$	-H	$-CF_3$

I266(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_3$
I267(a), (b), and (c)	O	$-CF_3$	-H	$-OCH_2CH_3$
I268(a), (b), and (c)	O	$-CF_3$	-H	$-OCF_3$
I269(a), (b), and (c)	O	$-CF_3$	-H	*-tert*-butyl
I270(a), (b), and (c)	O	$-CF_3$	-H	*-iso*-propyl
I271(a), (b), and (c)	O	$-CHF_2$	-Cl	-H
I272(a), (b), and (c)	O	$-CHF_2$	-Br	-H
I273(a), (b), and (c)	O	$-CHF_2$	-F	-H
I274(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	-H
I275(a), (b), and (c)	O	$-CHF_2$	$-CF_3$	-H
I276(a), (b), and (c)	O	$-CHF_2$	$-OCH_3$	-H
I277(a), (b), and (c)	O	$-CHF_2$	$-OCH_2CH_3$	-H
I278(a), (b), and (c)	O	$-CHF_2$	$-OCF_3$	-H
I279(a), (b), and (c)	O	$-CHF_2$	*-tert*-butyl	-H
I280(a), (b), and (c)	O	$-CHF_2$	*-iso*-propyl	-H
I281(a), (b), and (c)	O	$-CHF_2$	$-CH_3$	$-CH_3$
I282(a), (b), and (c)	O	$-CHF_2$	-H	-H
I283(a), (b), and (c)	O	$-CHF_2$	-H	-Cl
I284(a), (b), and (c)	O	$-CHF_2$	-H	-Br
I285(a), (b), and (c)	O	$-CHF_2$	-H	-F
I286(a), (b), and (c)	O	$-CHF_2$	-H	$-CH_3$
I287(a), (b), and (c)	O	$-CHF_2$	-H	$-CF_3$
I288(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_3$
I289(a), (b), and (c)	O	$-CHF_2$	-H	$-OCH_2CH_3$
I290(a), (b), and (c)	O	$-CHF_2$	-H	$-OCF_3$
I291(a), (b), and (c)	O	$-CHF_2$	-H	*-tert*-butyl
I292(a), (b), and (c)	O	$-CHF_2$	-H	*-iso*-propyl
I293(a), (b), and (c)	O	-OH	-Cl	-H
I294(a), (b), and (c)	O	-OH	-Br	-H
I295(a), (b), and (c)	O	-OH	-F	-H
I296(a), (b), and (c)	O	-OH	$-CH_3$	-H
I297(a), (b), and (c)	O	-OH	$-CF_3$	-H
I298(a), (b), and (c)	O	-OH	$-OCH_3$	-H
I299(a), (b), and (c)	O	-OH	$-OCH_2CH_3$	-H
I300(a), (b), and (c)	O	-OH	$-OCF_3$	-H
I301(a), (b), and (c)	O	-OH	*-tert*-butyl	-H
I302(a), (b), and (c)	O	-OH	*-iso*-propyl	-H
I303(a), (b), and (c)	O	-OH	$-CH_3$	$-CH_3$
I304(a), (b), and (c)	O	-OH	-H	-H
I305(a), (b), and (c)	O	-OH	-H	-Cl
I306(a), (b), and (c)	O	-OH	-H	-Br
I307(a), (b), and (c)	O	-OH	-H	-F
I308(a), (b), and (c)	O	-OH	-H	$-CH_3$
I309(a), (b), and (c)	O	-OH	-H	$-CF_3$
I310(a), (b), and (c)	O	-OH	-H	$-OCH_3$
I311(a), (b), and (c)	O	-OH	-H	$-OCH_2CH_3$
I312(a), (b), and (c)	O	-OH	-H	$-OCF_3$
I313(a), (b), and (c)	O	-OH	-H	*-tert*-butyl

I314(a), (b), and (c)	O	-OH	-H	-*iso*-propyl
I315(a), (b), and (c)	O	$-NO_2$	-Cl	-H
I316(a), (b), and (c)	O	$-NO_2$	-Br	-H
I317(a), (b), and (c)	O	$-NO_2$	-F	-H
I318(a), (b), and (c)	O	$-NO_2$	$-CH_3$	-H
I319(a), (b), and (c)	O	$-NO_2$	$-CF_3$	-H
I320(a), (b), and (c)	O	$-NO_2$	$-OCH_3$	-H
I321(a), (b), and (c)	O	$-NO_2$	$-OCH_2CH_3$	-H
I322(a), (b), and (c)	O	$-NO_2$	$-OCF_3$	-H
I323(a), (b), and (c)	O	$-NO_2$	-*tert*-butyl	-H
I324(a), (b), and (c)	O	$-NO_2$	-*iso*-propyl	-H
I325(a), (b), and (c)	O	$-NO_2$	$-CH_3$	$-CH_3$
I326(a), (b), and (c)	O	$-NO_2$	-H	-H
I327(a), (b), and (c)	O	$-NO_2$	-H	-Cl
I328(a), (b), and (c)	O	$-NO_2$	-H	-Br
I329(a), (b), and (c)	O	$-NO_2$	-H	-F
I330(a), (b), and (c)	O	$-NO_2$	-H	$-CH_3$
I331(a), (b), and (c)	O	$-NO_2$	-H	$-CF_3$
I332(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_3$
I333(a), (b), and (c)	O	$-NO_2$	-H	$-OCH_2CH_3$
I334(a), (b), and (c)	O	$-NO_2$	-H	$-OCF_3$
I335(a), (b), and (c)	O	$-NO_2$	-H	-*tert*-butyl
I336(a), (b), and (c)	O	$-NO_2$	-H	-*iso*-propyl
I337(a), (b), and (c)	O	-CN	-Br	-H
I338(a), (b), and (c)	O	-CN	-Cl	-H
I339(a), (b), and (c)	O	-CN	-F	-H
I340(a), (b), and (c)	O	-CN	$-CH_3$	-H
I341(a), (b), and (c)	O	-CN	$-CF_3$	-H
I342(a), (b), and (c)	O	-CN	$-OCH_3$	-H
I343(a), (b), and (c)	O	-CN	$-OCH_2CH_3$	-H
I344(a), (b), and (c)	O	-CN	$-OCF_3$	-H
I345(a), (b), and (c)	O	-CN	-*tert*-butyl	-H
I346(a), (b), and (c)	O	-CN	-*iso*-propyl	-H
I347(a), (b), and (c)	O	-CN	$-CH_3$	$-CH_3$
I348(a), (b), and (c)	O	-CN	-H	-H
I349(a), (b), and (c)	O	-CN	-H	-Cl
I350(a), (b), and (c)	O	-CN	-H	-Br
I351(a), (b), and (c)	O	-CN	-H	-F
I352(a), (b), and (c)	O	-CN	-H	$-CH_3$
I353(a), (b), and (c)	O	-CN	-H	$-CF_3$
I354(a), (b), and (c)	O	-CN	-H	$-OCH_3$
I355(a), (b), and (c)	O	-CN	-H	$-OCH_2CH_3$
I356(a), (b), and (c)	O	-CN	-H	$-OCF_3$
I357(a), (b), and (c)	O	-CN	-H	-*tert*-butyl
I358(a), (b), and (c)	O	-CN	-H	-*iso*-propyl
I359(a), (b), and (c)	O	-Br	-Br	-H
I360(a), (b), and (c)	O	-Br	-Cl	-H
I361(a), (b), and (c)	O	-Br	-F	-H

I362(a), (b), and (c)	O	-Br	$-CH_3$	-H
I363(a), (b), and (c)	O	-Br	$-CF_3$	-H
I364(a), (b), and (c)	O	-Br	$-OCH_3$	-H
I365(a), (b), and (c)	O	-Br	$-OCH_2CH_3$	-H
I366(a), (b), and (c)	O	-Br	$-OCF_3$	-H
I367(a), (b), and (c)	O	-Br	*-tert*-butyl	-H
I368(a), (b), and (c)	O	-Br	*-iso*-propyl	-H
I369(a), (b), and (c)	O	-Br	$-CH_3$	$-CH_3$
I370(a), (b), and (c)	O	-Br	-H	-H
I371(a), (b), and (c)	O	-Br	-H	-Cl
I372(a), (b), and (c)	O	-Br	-H	-Br
I373(a), (b), and (c)	O	-Br	-H	-F
I374(a), (b), and (c)	O	-Br	-H	$-CH_3$
I375(a), (b), and (c)	O	-Br	-H	$-CF_3$
I376(a), (b), and (c)	O	-Br	-H	$-OCH_3$
I377(a), (b), and (c)	O	-Br	-H	$-OCH_2CH_3$
I378(a), (b), and (c)	O	-Br	-H	$-OCF_3$
I379(a), (b), and (c)	O	-Br	-H	*-tert*-butyl
I380(a), (b), and (c)	O	-Br	-H	*-iso*-propyl
I381(a), (b), and (c)	O	-I	-Cl	-H
I382(a), (b), and (c)	O	-I	-Br	-H
I383(a), (b), and (c)	O	-I	-F	-H
I384(a), (b), and (c)	O	-I	$-CH_3$	-H
I385(a), (b), and (c)	O	-I	$-CF_3$	-H
I386(a), (b), and (c)	O	-I	$-OCH_3$	-H
I387(a), (b), and (c)	O	-I	$-OCH_2CH_3$	-H
I388(a), (b), and (c)	O	-I	$-OCF_3$	-H
I389(a), (b), and (c)	O	-I	*-tert*-butyl	-H
I390(a), (b), and (c)	O	-I	*-iso*-propyl	-H
I391(a), (b), and (c)	O	-I	$-CH_3$	$-CH_3$
I392(a), (b), and (c)	O	-I	-H	-H
I393(a), (b), and (c)	O	-I	-H	-Cl
I394(a), (b), and (c)	O	-I	-H	-Br
I395(a), (b), and (c)	O	-I	-H	-F
I396(a), (b), and (c)	O	-I	-H	$-CH_3$
I397(a), (b), and (c)	O	-I	-H	$-CF_3$
I398(a), (b), and (c)	O	-I	-H	$-OCH_3$
I399(a), (b), and (c)	O	-I	-H	$-OCH_2CH_3$
I400(a), (b), and (c)	O	-I	-H	$-OCF_3$
I401(a), (b), and (c)	O	-I	-H	*-tert*-butyl
I402(a), (b), and (c)	O	-I	-H	*-iso*-propyl
I403(a), (b), and (c)	NH	-Cl	-Cl	-H
I404(a), (b), and (c)	NH	-Cl	-Br	-H
I405(a), (b), and (c)	NH	-Cl	-F	-H
I406(a), (b), and (c)	NH	-Cl	$-CH_3$	-H
I407(a), (b), and (c)	NH	-Cl	$-CF_3$	-H
I408(a), (b), and (c)	NH	-Cl	$-OCH_3$	-H
I409(a), (b), and (c)	NH	-Cl	$-OCH_2CH_3$	-H

I410(a), (b), and (c)	NH	-Cl	$-OCF_3$	-H
I411(a), (b), and (c)	NH	-Cl	-*tert*-butyl	-H
I412(a), (b), and (c)	NH	-Cl	-*iso*-propyl	-H
I413(a), (b), and (c)	NH	-Cl	$-CH_3$	$-CH_3$
I414(a), (b), and (c)	NH	-Cl	-H	-H
I415(a), (b), and (c)	NH	-Cl	-H	$-CH_3$
I416(a), (b), and (c)	NH	-Cl	-H	-Cl
I417(a), (b), and (c)	NH	-Cl	-H	-Br
I418(a), (b), and (c)	NH	-Cl	-H	-F
I419(a), (b), and (c)	NH	-Cl	-H	$-CF_3$
I420(a), (b), and (c)	NH	-Cl	-H	$-OCH_3$
I421(a), (b), and (c)	NH	-Cl	-H	$-OCH_2CH_3$
I422(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
I423(a), (b), and (c)	NH	-Cl	-H	-*tert*-butyl
I424(a), (b), and (c)	NH	-Cl	-H	-*iso*-propyl
I425(a), (b), and (c)	NH	-Cl	-H	$-OCF_3$
I426(a), (b), and (c)	NH	-Cl	-H	-*tert*-butyl
I427(a), (b), and (c)	NH	-Cl	-H	-*iso*-propyl
I428(a), (b), and (c)	NH	$-CH_3$	-Cl	-H
I429(a), (b), and (c)	NH	$-CH_3$	-Br	-H
I430(a), (b), and (c)	NH	$-CH_3$	-F	-H
I431(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	-H
I432(a), (b), and (c)	NH	$-CH_3$	$-CF_3$	-H
I433(a), (b), and (c)	NH	$-CH_3$	$-OCH_3$	-H
I434(a), (b), and (c)	NH	$-CH_3$	$-OCH_2CH_3$	-H
I435(a), (b), and (c)	NH	$-CH_3$	$-OCF_3$	-H
I436(a), (b), and (c)	NH	$-CH_3$	-*tert*-butyl	-H
I437(a), (b), and (c)	NH	$-CH_3$	-*iso*-propyl	-H
I438(a), (b), and (c)	NH	$-CH_3$	$-CH_3$	$-CH_3$
I439(a), (b), and (c)	NH	$-CH_3$	-H	-H
I440(a), (b), and (c)	NH	$-CH_3$	-H	-Cl
I441(a), (b), and (c)	NH	$-CH_3$	-H	-Br
I442(a), (b), and (c)	NH	$-CH_3$	-H	-F
I443(a), (b), and (c)	NH	$-CH_3$	-H	$-CH_3$
I444(a), (b), and (c)	NH	$-CH_3$	-H	$-CF_3$
I445(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_3$
I446(a), (b), and (c)	NH	$-CH_3$	-H	$-OCH_2CH_3$
I447(a), (b), and (c)	NH	$-CH_3$	-H	$-OCF_3$
I448(a), (b), and (c)	NH	$-CH_3$	-H	-*tert*-butyl
I449(a), (b), and (c)	NH	$-CH_3$	-H	-*iso*-propyl
I450(a), (b), and (c)	NH	$-CF_3$	-Cl	-H
I451(a), (b), and (c)	NH	$-CF_3$	-Br	-H
I452(a), (b), and (c)	NH	$-CF_3$	-F	-H
I453(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	-H
I454(a), (b), and (c)	NH	$-CF_3$	$-CF_3$	-H
I455(a), (b), and (c)	NH	$-CF_3$	$-OCH_3$	-H
I456(a), (b), and (c)	NH	$-CF_3$	$-OCH_2CH_3$	-H
I457(a), (b), and (c)	NH	$-CF_3$	$-OCF_3$	-H

I458(a), (b), and (c)	NH	$-CF_3$	*-tert*-butyl	-H
I459(a), (b), and (c)	NH	$-CF_3$	*-iso*-propyl	-H
I460(a), (b), and (c)	NH	$-CF_3$	$-CH_3$	$-CH_3$
I461(a), (b), and (c)	NH	$-CF_3$	-H	-H
I462(a), (b), and (c)	NH	$-CF_3$	-H	-Cl
I463(a), (b), and (c)	NH	$-CF_3$	-H	-Br
I464(a), (b), and (c)	NH	$-CF_3$	-H	-F
I465(a), (b), and (c)	NH	$-CF_3$	-H	$-CH_3$
I466(a), (b), and (c)	NH	$-CF_3$	-H	$-CF_3$
I467(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_3$
I468(a), (b), and (c)	NH	$-CF_3$	-H	$-OCH_2CH_3$
I469(a), (b), and (c)	NH	$-CF_3$	-H	$-OCF_3$
I470(a), (b), and (c)	NH	$-CF_3$	-H	*-tert*-butyl
I471(a), (b), and (c)	NH	$-CF_3$	-H	*-iso*-propyl
I472(a), (b), and (c)	NH	$-CHF_2$	-Cl	-H
I473(a), (b), and (c)	NH	$-CHF_2$	-Br	-H
I474(a), (b), and (c)	NH	$-CHF_2$	-F	-H
I475(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	-H
I476(a), (b), and (c)	NH	$-CHF_2$	$-CF_3$	-H
I477(a), (b), and (c)	NH	$-CHF_2$	$-OCH_3$	-H
I478(a), (b), and (c)	NH	$-CHF_2$	$-OCH_2CH_3$	-H
I479(a), (b), and (c)	NH	$-CHF_2$	$-OCF_3$	-H
I480(a), (b), and (c)	NH	$-CHF_2$	*-tert*-butyl	-H
I481(a), (b), and (c)	NH	$-CHF_2$	*-iso*-propyl	-H
I482(a), (b), and (c)	NH	$-CHF_2$	$-CH_3$	$-CH_3$
I483(a), (b), and (c)	NH	$-CHF_2$	-H	-H
I484(a), (b), and (c)	NH	$-CHF_2$	-H	-Cl
I485(a), (b), and (c)	NH	$-CHF_2$	-H	-Br
I486(a), (b), and (c)	NH	$-CHF_2$	-H	-F
I487(a), (b), and (c)	NH	$-CHF_2$	-H	$-CH_3$
I488(a), (b), and (c)	NH	$-CHF_2$	-H	$-CF_3$
I489(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_3$
I490(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCH_2CH_3$
I491(a), (b), and (c)	NH	$-CHF_2$	-H	$-OCF_3$
I492(a), (b), and (c)	NH	$-CHF_2$	-H	*-tert*-butyl
I493(a), (b), and (c)	NH	$-CHF_2$	-H	*-iso*-propyl
I494(a), (b), and (c)	NH	-OH	-Cl	-H
I495(a), (b), and (c)	NH	-OH	-Br	-H
I496(a), (b), and (c)	NH	-OH	-F	-H
I497(a), (b), and (c)	NH	-OH	$-CH_3$	-H
I498(a), (b), and (c)	NH	-OH	$-CF_3$	-H
I499(a), (b), and (c)	NH	-OH	$-OCH_3$	-H
I500(a), (b), and (c)	NH	-OH	$-OCH_2CH_3$	-H
I501(a), (b), and (c)	NH	-OH	$-OCF_3$	-H
I502(a), (b), and (c)	NH	-OH	*-tert*-butyl	-H
I503(a), (b), and (c)	NH	-OH	*-iso*-propyl	-H
I504(a), (b), and (c)	NH	-OH	$-CH_3$	$-CH_3$
I505(a), (b), and (c)	NH	-OH	-H	-H

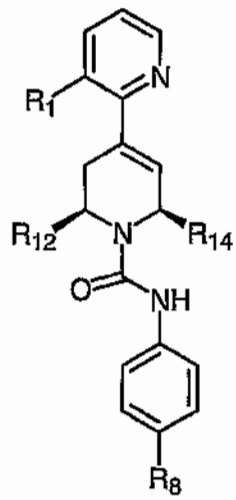
I506(a), (b), and (c)	NH	-OH	-H	-Cl
I507(a), (b), and (c)	NH	-OH	-H	-Br
I508(a), (b), and (c)	NH	-OH	-H	-F
I509(a), (b), and (c)	NH	-OH	-H	$-CH_3$
I510(a), (b), and (c)	NH	-OH	-H	$-CF_3$
I511(a), (b), and (c)	NH	-OH	-H	$-OCH_3$
I512(a), (b), and (c)	NH	-OH	-H	$-OCH_2CH_3$
I513(a), (b), and (c)	NH	-OH	-H	$-OCF_3$
I514(a), (b), and (c)	NH	-OH	-H	*-tert*-butyl
I515(a), (b), and (c)	NH	-OH	-H	*-iso*-propyl
I516(a), (b), and (c)	NH	$-NO_2$	-Cl	-H
I517(a), (b), and (c)	NH	$-NO_2$	-Br	-H
I518(a), (b), and (c)	NH	$-NO_2$	-F	-H
I519(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	-H
I520(a), (b), and (c)	NH	$-NO_2$	$-CF_3$	-H
I521(a), (b), and (c)	NH	$-NO_2$	$-OCH_3$	-H
I522(a), (b), and (c)	NH	$-NO_2$	$-OCH_2CH_3$	-H
I523(a), (b), and (c)	NH	$-NO_2$	$-OCF_3$	-H
I524(a), (b), and (c)	NH	$-NO_2$	*-tert*-butyl	-H
I525(a), (b), and (c)	NH	$-NO_2$	*-iso*-propyl	-H
I526(a), (b), and (c)	NH	$-NO_2$	$-CH_3$	$-CH_3$
I527(a), (b), and (c)	NH	$-NO_2$	-H	-H
I528(a), (b), and (c)	NH	$-NO_2$	-H	-Cl
I529(a), (b), and (c)	NH	$-NO_2$	-H	-Br
I530(a), (b), and (c)	NH	$-NO_2$	-H	-F
I531(a), (b), and (c)	NH	$-NO_2$	-H	$-CH_3$
I532(a), (b), and (c)	NH	$-NO_2$	-H	$-CF_3$
I533(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_3$
I534(a), (b), and (c)	NH	$-NO_2$	-H	$-OCH_2CH_3$
I535(a), (b), and (c)	NH	$-NO_2$	-H	$-OCF_3$
I536(a), (b), and (c)	NH	$-NO_2$	-H	*-tert*-butyl
I537(a), (b), and (c)	NH	$-NO_2$	-H	*-iso*-propyl
I538(a), (b), and (c)	NH	-CN	-Br	-H
I539(a), (b), and (c)	NH	-CN	-Cl	-H
I540(a), (b), and (c)	NH	-CN	-F	-H
I541(a), (b), and (c)	NH	-CN	$-CH_3$	-H
I542(a), (b), and (c)	NH	-CN	$-CF_3$	-H
I543(a), (b), and (c)	NH	-CN	$-OCH_3$	-H
I544(a), (b), and (c)	NH	-CN	$-OCH_2CH_3$	-H
I545(a), (b), and (c)	NH	-CN	$-OCF_3$	-H
I546(a), (b), and (c)	NH	-CN	*-tert*-butyl	-H
I547(a), (b), and (c)	NH	-CN	*-iso*-propyl	-H
I548(a), (b), and (c)	NH	-CN	$-CH_3$	$-CH_3$
I549(a), (b), and (c)	NH	-CN	-H	-H
I550(a), (b), and (c)	NH	-CN	-H	-Cl
I551(a), (b), and (c)	NH	-CN	-H	-Br
I552(a), (b), and (c)	NH	-CN	-H	-F
I553(a), (b), and (c)	NH	-CN	-H	$-CH_3$

I554(a), (b), and (c)	NH	-CN	-H	$-CF_3$
I555(a), (b), and (c)	NH	-CN	-H	$-OCH_3$
I556(a), (b), and (c)	NH	-CN	-H	$-OCH_2CH_3$
I557(a), (b), and (c)	NH	-CN	-H	$-OCF_3$
I558(a), (b), and (c)	NH	-CN	-H	-*tert*-butyl
I559(a), (b), and (c)	NH	-CN	-H	-*iso*-propyl
I560(a), (b), and (c)	NH	-Br	-Br	-H
I561(a), (b), and (c)	NH	-Br	-Cl	-H
I562(a), (b), and (c)	NH	-Br	-F	-H
I563(a), (b), and (c)	NH	-Br	$-CH_3$	-H
I564(a), (b), and (c)	NH	-Br	$-CF_3$	-H
I565(a), (b), and (c)	NH	-Br	$-OCH_3$	-H
I566(a), (b), and (c)	NH	-Br	$-OCH_2CH_3$	-H
I567(a), (b), and (c)	NH	-Br	$-OCF_3$	-H
I568(a), (b), and (c)	NH	-Br	-*tert*-butyl	-H
I569(a), (b), and (c)	NH	-Br	-*iso*-propyl	-H
I570(a), (b), and (c)	NH	-Br	$-CH_3$	$-CH_3$
I571(a), (b), and (c)	NH	-Br	-H	-H
I572(a), (b), and (c)	NH	-Br	-H	-Cl
I573(a), (b), and (c)	NH	-Br	-H	-Br
I574(a), (b), and (c)	NH	-Br	-H	-F
I575(a), (b), and (c)	NH	-Br	-H	$-CH_3$
I576(a), (b), and (c)	NH	-Br	-H	$-CF_3$
I577(a), (b), and (c)	NH	-Br	-H	$-OCH_3$
I578(a), (b), and (c)	NH	-Br	-H	$-OCH_2CH_3$
I579(a), (b), and (c)	NH	-Br	-H	$-OCF_3$
I580(a), (b), and (c)	NH	-Br	-H	-*tert*-butyl
I581(a), (b), and (c)	NH	-Br	-H	-*iso*-propyl
I582(a), (b), and (c)	NH	-I	-Cl	-H
I583(a), (b), and (c)	NH	-I	-Br	-H
I584(a), (b), and (c)	NH	-I	-F	-H
I585(a), (b), and (c)	NH	-I	$-CH_3$	-H
I586(a), (b), and (c)	NH	-I	$-CF_3$	-H
I587(a), (b), and (c)	NH	-I	$-OCH_3$	-H
I588(a), (b), and (c)	NH	-I	$-OCH_2CH_3$	-H
I589(a), (b), and (c)	NH	-I	$-OCF_3$	-H
I590(a), (b), and (c)	NH	-I	-*tert*-butyl	-H
I591(a), (b), and (c)	NH	-I	-*iso*-propyl	-H
I592(a), (b), and (c)	NH	-I	$-CH_3$	$-CH_3$
I593(a), (b), and (c)	NH	-I	-H	-H
I594(a), (b), and (c)	NH	-I	-H	-Cl
I595(a), (b), and (c)	NH	-I	-H	-Br
I596(a), (b), and (c)	NH	-I	-H	-F
I597(a), (b), and (c)	NH	-I	-H	$-CH_3$
I598(a), (b), and (c)	NH	-I	-H	$-CF_3$
I599(a), (b), and (c)	NH	-I	-H	$-OCH_3$
I600(a), (b), and (c)	NH	-I	-H	$-OCH_2CH_3$
I601(a), (b), and (c)	NH	-I	-H	$-OCF_3$

I602(a), (b), and (c)	NH	-I	-H	-*tert*-butyl
I603(a), (b), and (c)	NH	-I	-H	-*iso*-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

Table 10



(IIb)

and pharmaceutically acceptable salts thereof, where:

Compound	R_1	R_8
J01(a), (b), and (c)	-Cl	-H
J02(a), (b), and (c)	-Cl	-t-butyl
J03(a), (b), and (c)	-Cl	-iso-butyl
J04(a), (b), and (c)	-Cl	-*sec*-butyl
J05(a), (b), and (c)	-Cl	-iso-propyl
J06(a), (b), and (c)	-Cl	-n-propyl
J07(a), (b), and (c)	-Cl	-cyclohexyl
J08(a), (b), and (c)	-Cl	-t-butoxy
J09(a), (b), and (c)	-Cl	-*iso*-propoxy
J10(a), (b), and (c)	-Cl	$-CF_3$
J11(a), (b), and (c)	-Cl	$-CH_2CF_3$
J12(a), (b), and (c)	-Cl	$-OCF_3$
J13(a), (b), and (c)	-Cl	-Cl
J14(a), (b), and (c)	-Cl	-Br
J15(a), (b), and (c)	-Cl	-I
J16(a), (b), and (c)	-Cl	-n-butyl
J17(a), (b), and (c)	-Cl	-n-propyl
J18(a), (b), and (c)	-F	-H
J19(a), (b), and (c)	-F	-t-butyl
J20(a), (b), and (c)	-F	-iso-butyl
J21(a), (b), and (c)	-F	-*sec*-butyl
J22(a), (b), and (c)	-F	-iso-propyl
J23(a), (b), and (c)	-F	-n-propyl
J24(a), (b), and (c)	-F	-cyclohexyl
J25(a), (b), and (c)	-F	-t-butoxy
J26(a), (b), and (c)	-F	-*iso*-propoxy

J27(a), (b), and (c)	-F	$-CF_3$
J28(a), (b), and (c)	-F	$-CH_2CF_3$
J29(a), (b), and (c)	-F	$-OCF_3$
J30(a), (b), and (c)	-F	-Cl
J31(a), (b), and (c)	-F	-Br
J32(a), (b), and (c)	-F	-I
J33(a), (b), and (c)	-F	-n-butyl
J34(a), (b), and (c)	-F	-n-propyl
J35(a), (b), and (c)	$-CH_3$	-H
J36(a), (b), and (c)	$-CH_3$	-iso-butyl
J37(a), (b), and (c)	$-CH_3$	-t-butyl
J38(a), (b), and (c)	$-CH_3$	-*sec*-butyl
J39(a), (b), and (c)	$-CH_3$	-iso-propyl
J40(a), (b), and (c)	$-CH_3$	-n-propyl
J41(a), (b), and (c)	$-CH_3$	-cyclohexyl
J42(a), (b), and (c)	$-CH_3$	-t-butoxy
J43(a), (b), and (c)	$-CH_3$	-*iso*-propoxy
J44(a), (b), and (c)	$-CH_3$	$-CF_3$
J45(a), (b), and (c)	$-CH_3$	$-CH_2CF_3$
J46(a), (b), and (c)	$-CH_3$	$-OCF_3$
J47(a), (b), and (c)	$-CH_3$	-Cl
J48(a), (b), and (c)	$-CH_3$	-Br
J49(a), (b), and (c)	$-CH_3$	-I
J50(a), (b), and (c)	$-CH_3$	-n-butyl
J51(a), (b), and (c)	$-CH_3$	-n-propyl
J52(a), (b), and (c)	$-CF_3$	-H
J53(a), (b), and (c)	$-CF_3$	-t-butyl
J54(a), (b), and (c)	$-CF_3$	-iso-butyl
J55(a), (b), and (c)	$-CF_3$	-*sec*-butyl
J56(a), (b), and (c)	$-CF_3$	-iso-propyl
J57(a), (b), and (c)	$-CF_3$	-n-propyl
J58(a), (b), and (c)	$-CF_3$	-cyclohexyl
J59(a), (b), and (c)	$-CF_3$	-t-butoxy
J60(a), (b), and (c)	$-CF_3$	-*iso*-propoxy
J61(a), (b), and (c)	$-CF_3$	$-CF_3$
J62(a), (b), and (c)	$-CF_3$	$-CH_2CF_3$
J63(a), (b), and (c)	$-CF_3$	$-OCF_3$
J64(a), (b), and (c)	$-CF_3$	-Cl
J65(a), (b), and (c)	$-CF_3$	-Br
J66(a), (b), and (c)	$-CF_3$	-I
J67(a), (b), and (c)	$-CF_3$	-n-butyl
J68(a), (b), and (c)	$-CF_3$	-n-propyl
J69(a), (b), and (c)	$-CHF_2$	-t-butyl
J70(a), (b), and (c)	$-CHF_2$	-H
J71(a), (b), and (c)	$-CHF_2$	-iso-butyl
J72(a), (b), and (c)	$-CHF_2$	-*sec*-butyl
J73(a), (b), and (c)	$-CHF_2$	-iso-propyl
J74(a), (b), and (c)	$-CHF_2$	-n-propyl

J75(a), (b), and (c)	$-CHF_2$	-cyclohexyl
J76(a), (b), and (c)	$-CHF_2$	-t-butoxy
J77(a), (b), and (c)	$-CHF_2$	-*iso*-propoxy
J78(a), (b), and (c)	$-CHF_2$	$-CF_3$
J79(a), (b), and (c)	$-CHF_2$	$-CH_2CF_3$
J80(a), (b), and (c)	$-CHF_2$	$-OCF_3$
J81(a), (b), and (c)	$-CHF_2$	-Cl
J82(a), (b), and (c)	$-CHF_2$	-Br
J83(a), (b), and (c)	$-CHF_2$	-I
J84(a), (b), and (c)	$-CHF_2$	-n-butyl
J85(a), (b), and (c)	$-CHF_2$	-n-propyl
J86(a), (b), and (c)	-OH	-H
J87(a), (b), and (c)	-OH	-t-butyl
J88(a), (b), and (c)	-OH	-iso-butyl
J89(a), (b), and (c)	-OH	-*sec*-butyl
J90(a), (b), and (c)	-OH	-iso-propyl
J91(a), (b), and (c)	-OH	-n-propyl
J92(a), (b), and (c)	-OH	-cyclohexyl
J93(a), (b), and (c)	-OH	-t-butoxy
J94(a), (b), and (c)	-OH	-*iso*-propoxy
J95(a), (b), and (c)	-OH	$-CF_3$
J96(a), (b), and (c)	-OH	$-CH_2CF_3$
J97(a), (b), and (c)	-OH	$-OCF_3$
J98(a), (b), and (c)	-OH	-Cl
J99(a), (b), and (c)	-OH	-Br
J100(a), (b), and (c)	-OH	-I
J101(a), (b), and (c)	-OH	-n-butyl
J102(a), (b), and (c)	-OH	-n-propyl
J103(a), (b), and (c)	$-NO_2$	-H
J104(a), (b), and (c)	$-NO_2$	-t-butyl
J105(a), (b), and (c)	$-NO_2$	-iso-butyl
J106(a), (b), and (c)	$-NO_2$	-*sec*-butyl
J107(a), (b), and (c)	$-NO_2$	-iso-propyl
J108(a), (b), and (c)	$-NO_2$	-n-propyl
J109(a), (b), and (c)	$-NO_2$	-cyclohexyl
J110(a), (b), and (c)	$-NO_2$	-t-butoxy
J111(a), (b), and (c)	$-NO_2$	-*iso*-propoxy
J112(a), (b), and (c)	$-NO_2$	$-CF_3$
J113(a), (b), and (c)	$-NO_2$	$-CH_2CF_3$
J114(a), (b), and (c)	$-NO_2$	$-OCF_3$
J115(a), (b), and (c)	$-NO_2$	-Cl
J116(a), (b), and (c)	$-NO_2$	-Br
J117(a), (b), and (c)	$-NO_2$	-I
J118(a), (b), and (c)	$-NO_2$	-n-butyl
J119(a), (b), and (c)	$-NO_2$	-n-propyl
J120(a), (b), and (c)	-CN	-H
J121(a), (b), and (c)	-CN	-t-butyl
J122(a), (b), and (c)	-CN	-iso-butyl

J123(a), (b), and (c)	-CN	-*sec*-butyl
J124(a), (b), and (c)	-CN	-iso-propyl
J125(a), (b), and (c)	-CN	-n-propyl
J126(a), (b), and (c)	-CN	-cyclohexyl
J127(a), (b), and (c)	-CN	-t-butoxy
J128(a), (b), and (c)	-CN	-*iso*-propoxy
J129(a), (b), and (c)	-CN	$-CF_3$
J130(a), (b), and (c)	-CN	$-CH_2CF_3$
J131(a), (b), and (c)	-CN	$-OCF_3$
J132(a), (b), and (c)	-CN	-Cl
J133(a), (b), and (c)	-CN	-Br
J134(a), (b), and (c)	-CN	-I
J135(a), (b), and (c)	-CN	-n-butyl
J136(a), (b), and (c)	-CN	-n-propyl
J137(a), (b), and (c)	-Br	-H
J138(a), (b), and (c)	-Br	-t-butyl
J139(a), (b), and (c)	-Br	-iso-butyl
J140(a), (b), and (c)	-Br	-*sec*-butyl
J141(a), (b), and (c)	-Br	-iso-propyl
J142(a), (b), and (c)	-Br	-n-propyl
J143(a), (b), and (c)	-Br	-cyclohexyl
J144(a), (b), and (c)	-Br	-t-butoxy
J145(a), (b), and (c)	-Br	-*iso*-propoxy
J146(a), (b), and (c)	-Br	$-CF_3$
J147(a), (b), and (c)	-Br	$-CH_2CF_3$
J148(a), (b), and (c)	-Br	$-OCF_3$
J149(a), (b), and (c)	-Br	-Cl
J150(a), (b), and (c)	-Br	-Br
J151(a), (b), and (c)	-Br	-I
J152(a), (b), and (c)	-Br	-n-butyl
J153(a), (b), and (c)	-Br	-n-propyl
J154(a), (b), and (c)	-I	-t-butyl
J155(a), (b), and (c)	-I	-H
J156(a), (b), and (c)	-I	-iso-butyl
J157(a), (b), and (c)	-I	-*sec*-butyl
J158(a), (b), and (c)	-I	-iso-propyl
J159(a), (b), and (c)	-I	-n-propyl
J160(a), (b), and (c)	-I	-cyclohexyl
J161(a), (b), and (c)	-I	-t-butoxy
J162(a), (b), and (c)	-I	-*iso*-propoxy
J163(a), (b), and (c)	-I	$-CF_3$
J164(a), (b), and (c)	-I	$-CH_2CF_3$
J165(a), (b), and (c)	-I	$-OCF_3$
J166(a), (b), and (c)	-I	-Cl
J167(a), (b), and (c)	-I	-Br
J168(a), (b), and (c)	-I	-I
J169(a), (b), and (c)	-I	-n-butyl
J170(a), (b), and (c)	-I	-n-propyl

(a) means that R_{12} is -H and R_{14} is $-CH_3$.
(b) means that R_{12} is $-CH_3$ and R_{14} is -H.
(c) means that R_{12} and R_{14} are each -H.

4.3 DEFINITIONS

As used in connection with the Tetrahydropiperidyl Compounds 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)heterocycle can be attached via a nitrogen or carbon atom. Representative -(3- to 7-membered)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrimidinyl, 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)heterocycle can be attached via a nitrogen or carbon atom. Representative -(3- to 5-membered)heterocycles 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, pyrimidinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

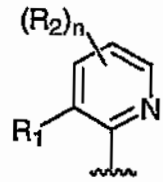
"-CH_2(halo)" means a methyl group where one of the hydrogens of the methyl group has been replaced with a halogen. Representative -CH_2(halo) groups include -CH_2F, -CH_2Cl, -CH_2Br, and -CH_2I.

"-$CH(halo)_2$" 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.

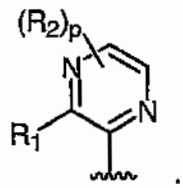
"-Halogen" or "-halo" means -F, -Cl, -Br, or -I.

The phrase "pyridyl group" means



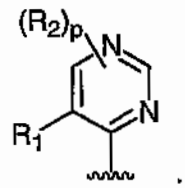
where R_1, R_2, and n are defined above for the Tetrahydropiperidyl Compounds of formula (II).

The phrase "pyrazinyl group" means,



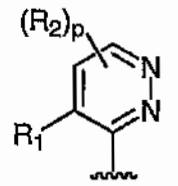
where R_1, R_2, and p are defined above for the Tetrahydropiperidyl Compounds of formula (I).

The phrase "pyrimidinyl group" means



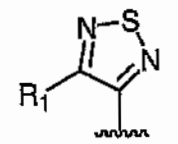
where R_1, R_2, and p are defined above for the Tetrahydropiperidyl Compounds of formula (I).

The phrase "pyridazinyl group" means



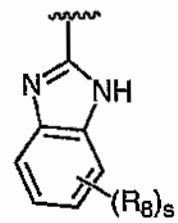
where R_1, R_2, and p are defined above for the Tetrahydropiperidyl Compounds of formula (I).

The phrase "thiadiazolyl group" means



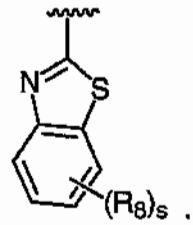
where R_1 is defined above for the Tetrahydropiperidyl Compounds of formula (I).

The phrase "benzoimidiazolyl group " means



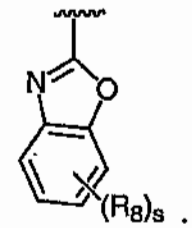
where R_8 and s is defined above for the Tetrahydropiperidyl Compounds of formula (I) or (II).

The phrase "benzothiazolyl group" means



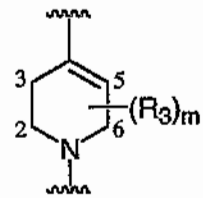
where R_8 and s is defined above for the Tetrahydropiperidyl Compounds of formula (I) or (II).

The phrase "benzooxazolyl group" means



where R_8 and s is defined above for the Tetrahydropiperidyl Compounds of formula (I) or (II).

The phrase "Tetrahydropiperidyl ring" means



where the numbers designate the position of each atom of the Tetrahydropiperidyl ring.

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 Tetrahydropiperidyl Compound, including a salt formed from an acid and a basic functional group, such as a nitrogen group, of one of the Tetrahydropiperidyl 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, glucoronate, 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 diethylaminosulfur 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 term "LiHMDS" means lithium hexamethyldisilazide.

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.

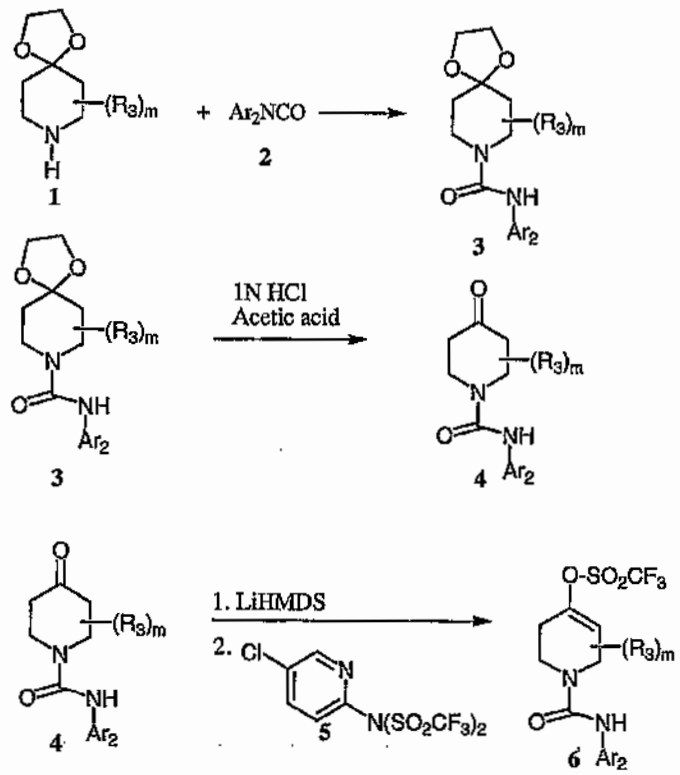
4.4 METHODS FOR MAKING THE TETRAHYDROPIPERIDYL COMPOUNDS

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

4.4.1 Methods for Making the Tetrahydropiperidyl Compounds Where X is O

The Tetrahydropiperidyl Compounds where X is O can be obtained by the following illustrative method shown below in Schemes **1** and **2.**

Scheme 1



where R_3, Ar_2, and m, are defined above.

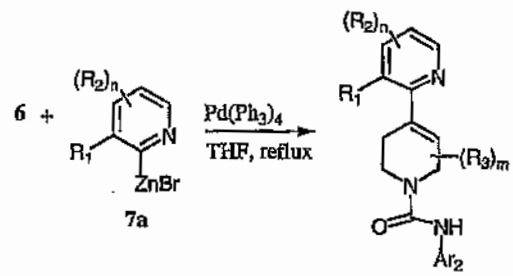
To a solution of ketal **1** (about 14 mmol) in DCM (about 7 mL) is added an isocyanate of formula Ar_2-NCO (about 14 mmol) **2** and the resulting solution is allowed to stir at about 25°C. Typically, the reaction mixture is allowed to stir for at least 5 min. The solvent is then removed to provide a compound of formula **3**, which is dissolved in THF (about 20 mL). About 1 N HCl in acetic acid (about 30 mL) is added to the THF solution of the compound of formula **3**, and the resulting mixture is heated at the reflux temperature of the solvent. Typically, the reaction mixture is heated at the reflux temperature of the solvent for about 3 h. The reaction mixture is then cooled and the solvent is removed to provide a residue that is dissolved in DCM. The DCM solution is then extracted with aq. Na_2CO_3, the aqueous and organic layers are separated, and the organic layer is extracted three times with DCM. The organic layers are combined, dried with $MgSO_4$, and the solvent is removed to provide a compound of formula **4**. The compound of formula **4** can be purified. In one embodiment, the compound of formula **4** is purified using silica gel column chromatography.

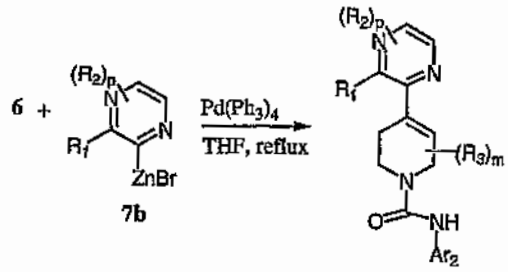
The compound of formula **4** (about 3.6 mmol) is then dissolved in THF (about 100 mL) and the resulting solution cooled to about -78°C. To the cooled solution is

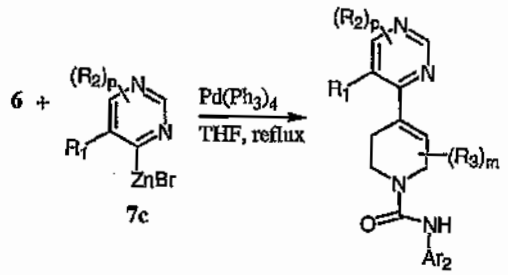
added LiHMDS (about 8.75 mmol) and the reaction mixture is stirred at about -78°C for about 2 h. A compound of formula **5** (about 3.6 mmol, commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) is then added to the reaction mixture and the reaction mixture is stirred at about -78°C for about 2 h. The reaction mixture is then allowed to warm to about 25°C and the solvent is removed to provide a compound of formula **6**. The compound of formula **6** can be purified.

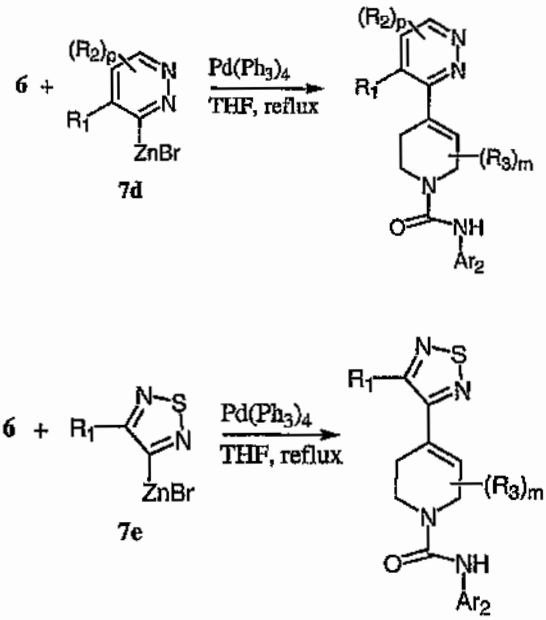
The compound of formula **6** is then reacted with a compound of formula **7a-e** to provide the Tetrahydropiperidyl Compound where X is O as shown below in Scheme **2.**

Scheme 2









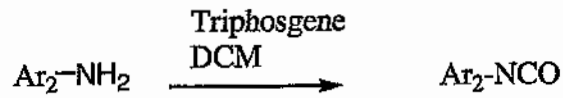
where R_1, R_2, R_3, Ar_1, n, m, and p are defined above.

$Pd(PPh)_3$ (0.11 mmol) is dissolved in THF (about 50 mL) and the compound of formula **6** (about 2.2 mmol) is added to the resulting solution followed by a compound of formula **7a-e** (about 6.6 mmol as a 0.5 M solution in THF). The resulting reaction mixture is then heated for about 1 h at the reflux temperature of the solvent. The reaction mixture is allowed to cool to about 25°C and the solvent is removed to provide the Tetrahydropiperidyl Compound where X is O. The Tetrahydropiperidyl Compound where X is O can be purified. In one embodiment, the Tetrahydropiperidyl Compound where X is O is purified using silica gel column chromatography followed by trituration with ethyl acetate.

Where m = 1, a mixture of Tetrahydropiperidyl compounds is generally obtained. The mixture can be separated via conventional methods, for example, column chromatography.

The compounds of formula **1** are commercially available or can be obtained by methods known to those skilled in the art.

Isocyanates of formula Ar_2-NCO, **2**, are commercially available or are preparable by reacting an amine Ar_2NH_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.

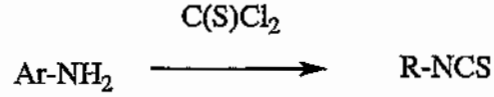
The compounds of formula **7a-e** can be obtained by methods known to those skilled in the art.

4.4.2 Methods for Making the Tetrahydropiperidyl Compounds Where X is S

The Tetrahydropiperidyl Compounds where X is S can be obtained by methods analagous to that described in Schemes **1** and **2** to provide the Tetrahydropiperidyl Compounds where X is O, except that an isothiocyanate of formula Ar_2-NCS is used in place of the isocyanate Ar_2-NCO.

Where m = 1, a mixture of Tetrahydropiperidyl compounds is generally obtained. The mixture can be separated via conventional methods, for example, column chromatography.

Isothiocyanates are commercially available or preparable by reacting an amine of formula Ar_2NH_2 with thiophosgene as shown in the scheme below (See, e.g., *Tetrahedron 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 *Tetrahedron. Lett.*, 42(32):5414-5416 (2001).



Alternatively, isothiocyanates of formula Ar_2-NCS can be prepared by reacting an amine of formula Ar_2NH_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)).

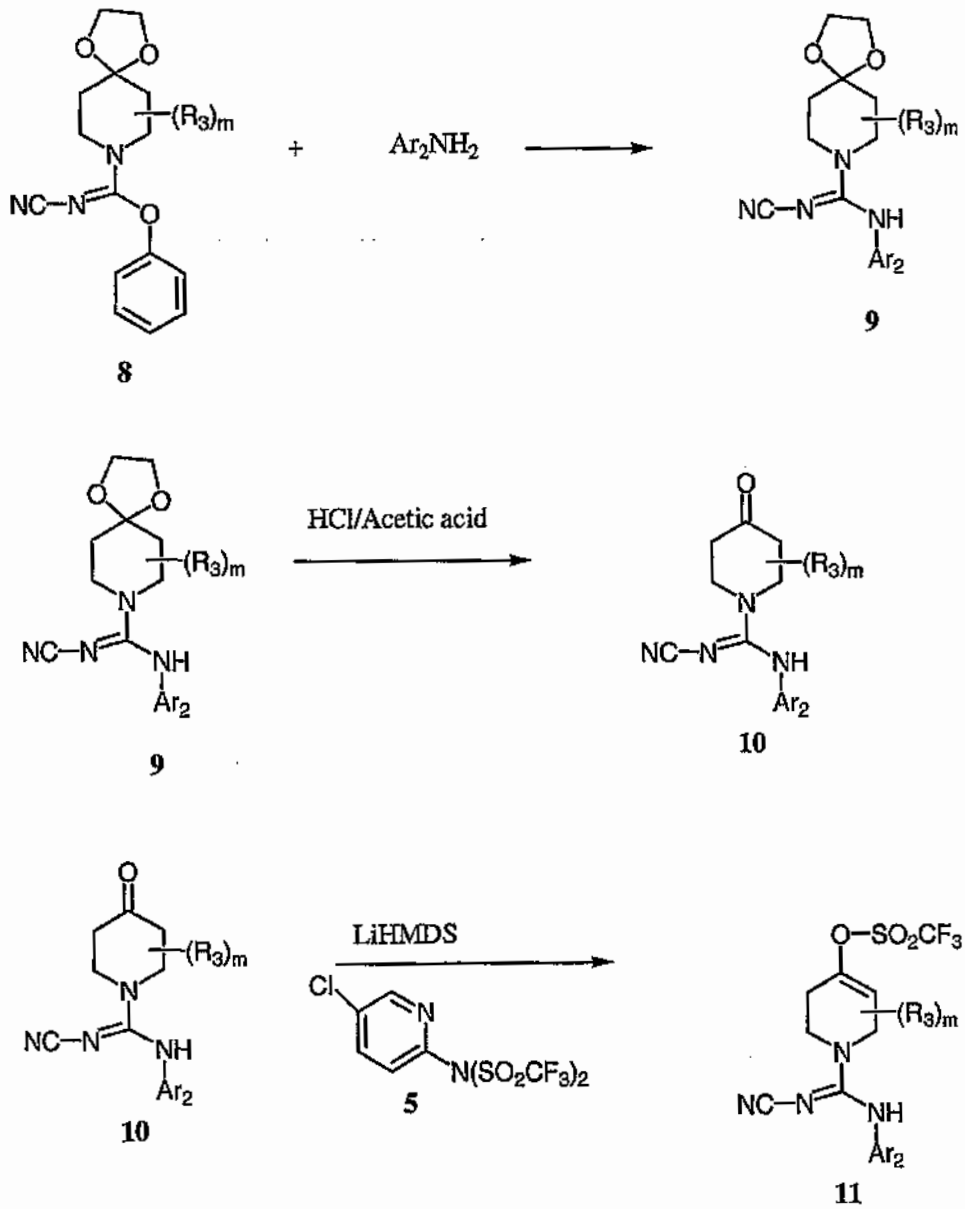
1. Et_3N, THF, CS_2
2. H_2O_2
3. HCl, water

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

4.4.3 Methods for Making the Tetrahydropiperidyl Compounds Where X is N-CN

The Tetrahydropiperidyl Compounds where X is N-CN can be obtained as shown below in Schemes **3** and **4**.

Scheme 3



where Ar_2, R_3, and m are defined above for the Tetrahydropiperidyl Compounds.

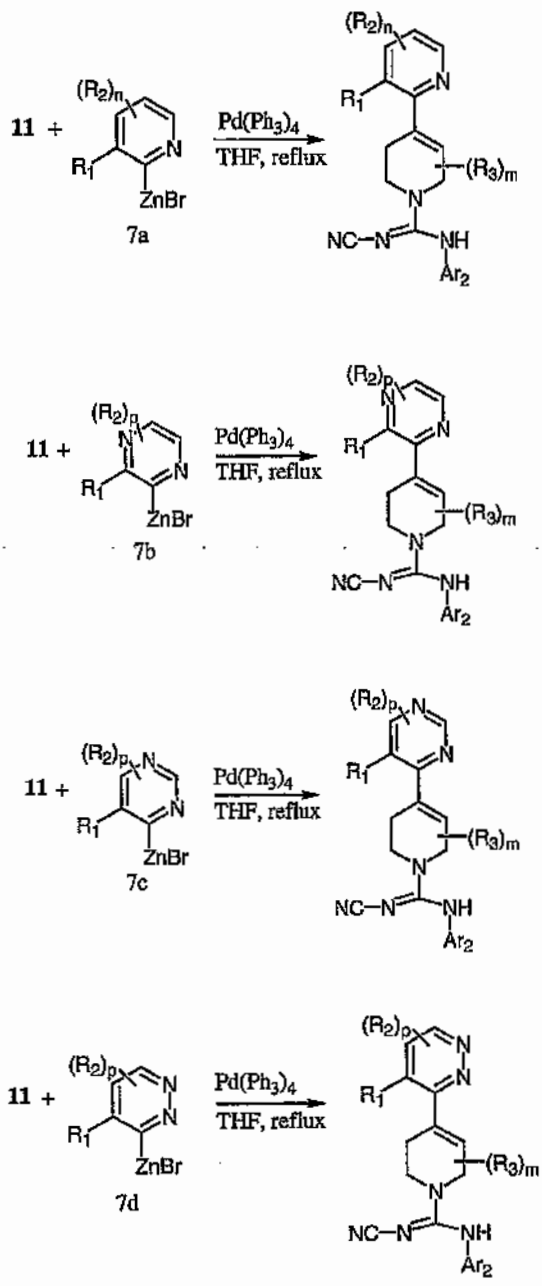
A ketal of formula **8** (about 14 mmol) is reacted with an amine of formula Ar-NH_2 (about 14 mmol) in an aprotic organic solvent (about 7 mL) such as diethyl ether, di-n-propyl ether, THF, DCM, or toluene at a temperature ranging from about about 25°C to about the reflux temperature of the solvent for a period of about 0.5 h to about 24 h. The solvent is then removed to provide a compound of formula **9**. 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 **8** and the amine of formula Ar-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 8 and the amine of formula Ar-NH_2 is heated at a temperature of about at 75°C for about 12 h.

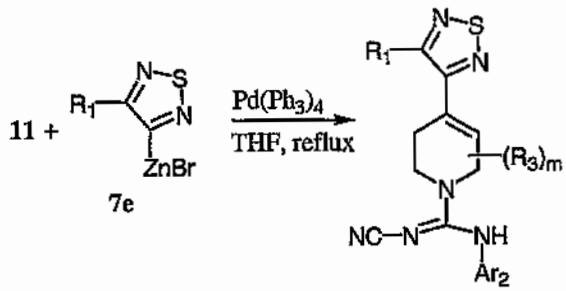
The compound of formula **9** is then dissolved in THF (about 20 mL). About 1 N HCl in acetic acid (about 30 mL) is added to the THF solution of the compound of formula **9** and the resulting mixture is heated at the reflux temperature of the solvent. Typically, the reaction mixture is heated at the reflux temperature of the solvent for about 3 h. The reaction mixture is then cooled and the solvent is removed to provide a residue that is dissolved in DCM. The DCM solution is then extracted with aq. Na_2CO_3, the aqueous and organic layer is separated, and the aqueous layer is extracted three times with DCM. The combined organic layers are then dried with $MgSO_4$ and the solvent removed to provide a compound of formula **10**. The compound of formula **10** can be purified. In one embodiment, the compound of formula **10** is purified using silica gel column chromatography.

The compound of formula **10** (about 3.6 mmol) is then dissolved in THF (about 100 mL) and the resulting solution cooled to about -78°C. To the cooled solution is added LiHMDS (about 8.75 mmol) and the reaction mixture is stirred at about -78°C for about 2 h. A compound of formula **5** (about 3.6 mmol, commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) is then added to the reaction mixture and the reaction mixture stirred at about -78°C for about 2 h. The reaction mixture is then allowed to warm to about 25°C and the solvent is removed to provide a compound of formula **11**. The compound of formula **11** can be purified.

The compound of formula **11** is then reacted with a compound of formula **7a-e** as shown below in Scheme **4** to provide the Tetrahydropiperidyl Compound where X is N-CN.

Scheme 4





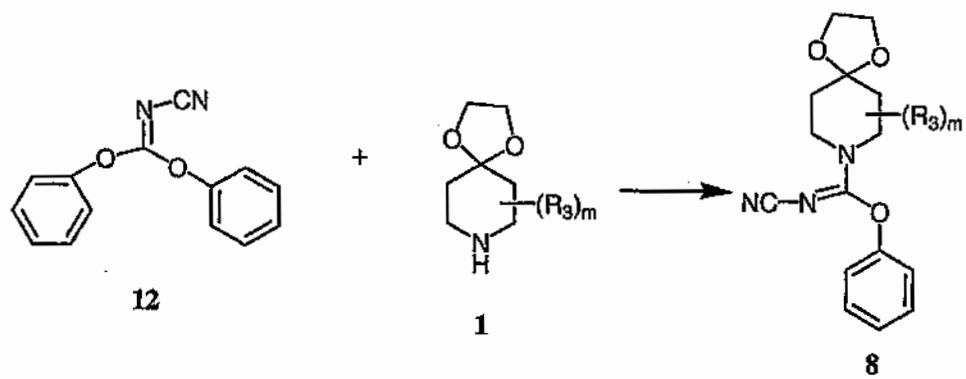
where Ar_2, R_1, R_2, R_3, n, m, and p are defined above for the Tetrahydropiperidyl Compounds.

$Pd(PPh)_3$ is dissolved in THF (about 50 mL) and the compound of formula **11** (about 2.2 mmol) is added to the resulting mixture followed by a compound of formula **7a-e** (about 6.6 mmol as a 0.5 M solution in THF. The resulting reaction mixture is then heated for about 1 h at the reflux temperature of the solvent. The reaction mixture is allowed to cool to about 25°C and the solvent removed to provide the Tetrahydropiperidyl Compound where X is N-CN. The Tetrahydropiperidyl Compound where X is N-CN can be purified. In one embodiment, the Tetrahydropiperidyl Compound where X is N-CN is purified by silica gel column chromatography.

Where m = 1, a mixture of Tetrahydropiperidyl compounds is generally obtained. The mixture can be separated via conventional methods, for example, column chromatography.

The compound of formula **8** can be obtained as shown below in Scheme **5.**

Scheme 5



where R_3, and m are defined above for the Tetrahydropiperidyl Compounds.

A compound of formula **1** is reacted with diphenylcyanocarbonimidate **12** (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com))

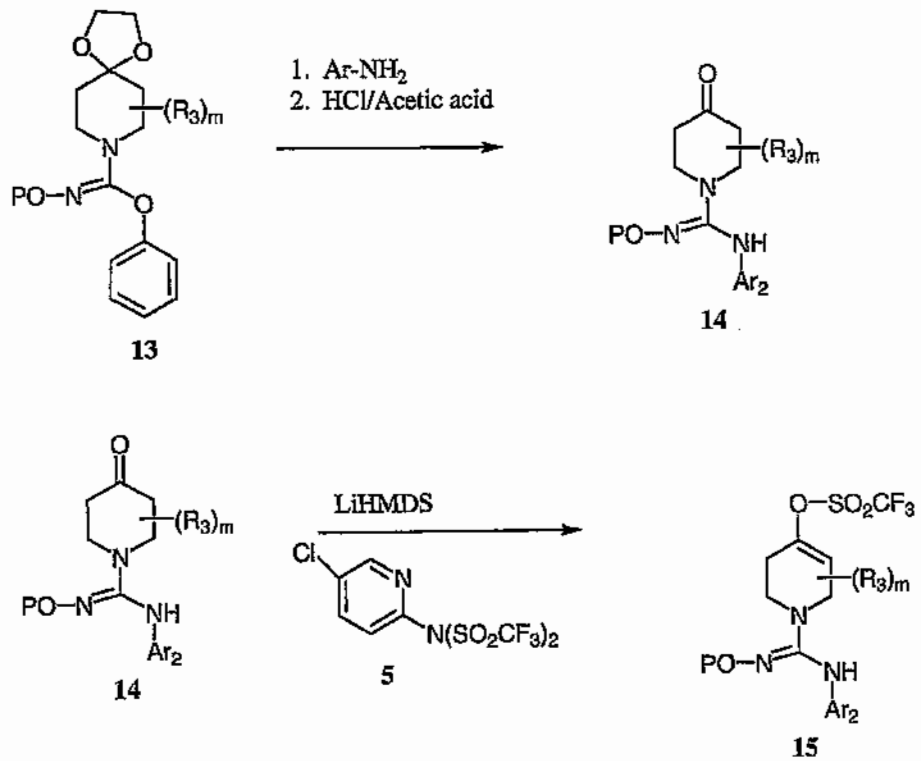
in an aprotic solvent such as diethyl ether, di-n-propyl ether, THF, DCM, or toluene to provide the compound of formula **8**. In one embodiment, the aprotic solvent is DCM and the reaction mixture of the compound of formula **1** and diphenylcyanocabonimidate **12** is allowed to react at about about 25°C. In another embodiment, the aprotic solvent is toluene and the reaction mixture of the compound of formula **1** and diphenylcyanocabonimidate **12** is allowed to react at about 110°C. The compound of formula **1** and diphenylcyanocabonimidate **12** is typically allowed to react for a period of about 0.5 h to about 24 h.

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

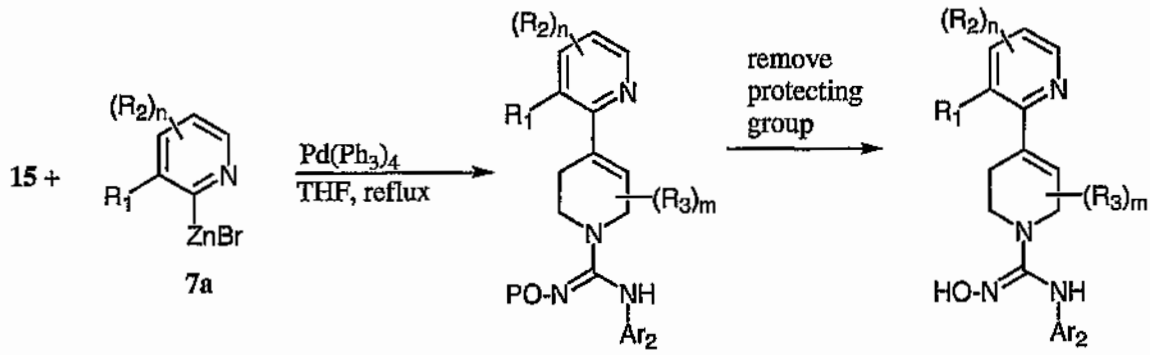
4.4.4 Methods for Making the Tetrahydropiperidyl Compounds Where X is N-OH

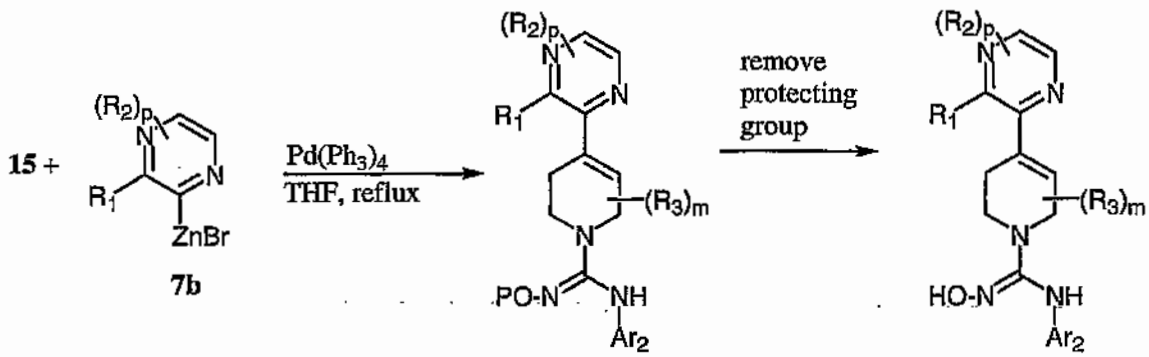
The Tetrahydropiperidyl Compounds where X is N-OH can be obtained as described below in Scheme **6.**

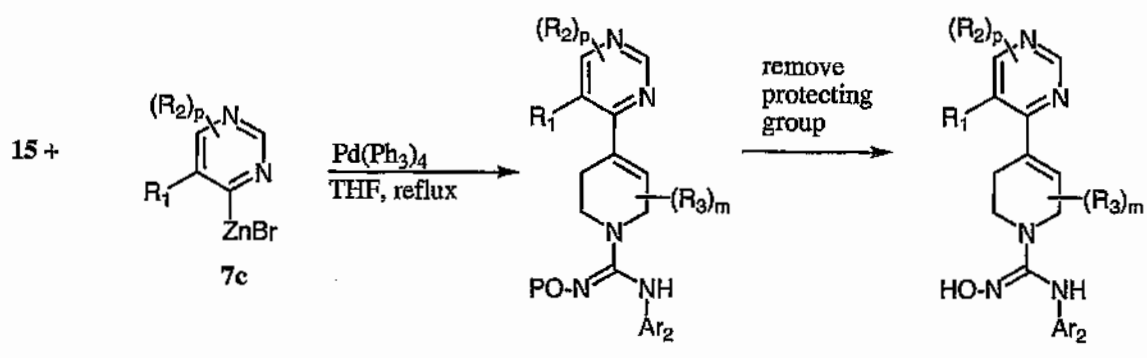
Scheme 6

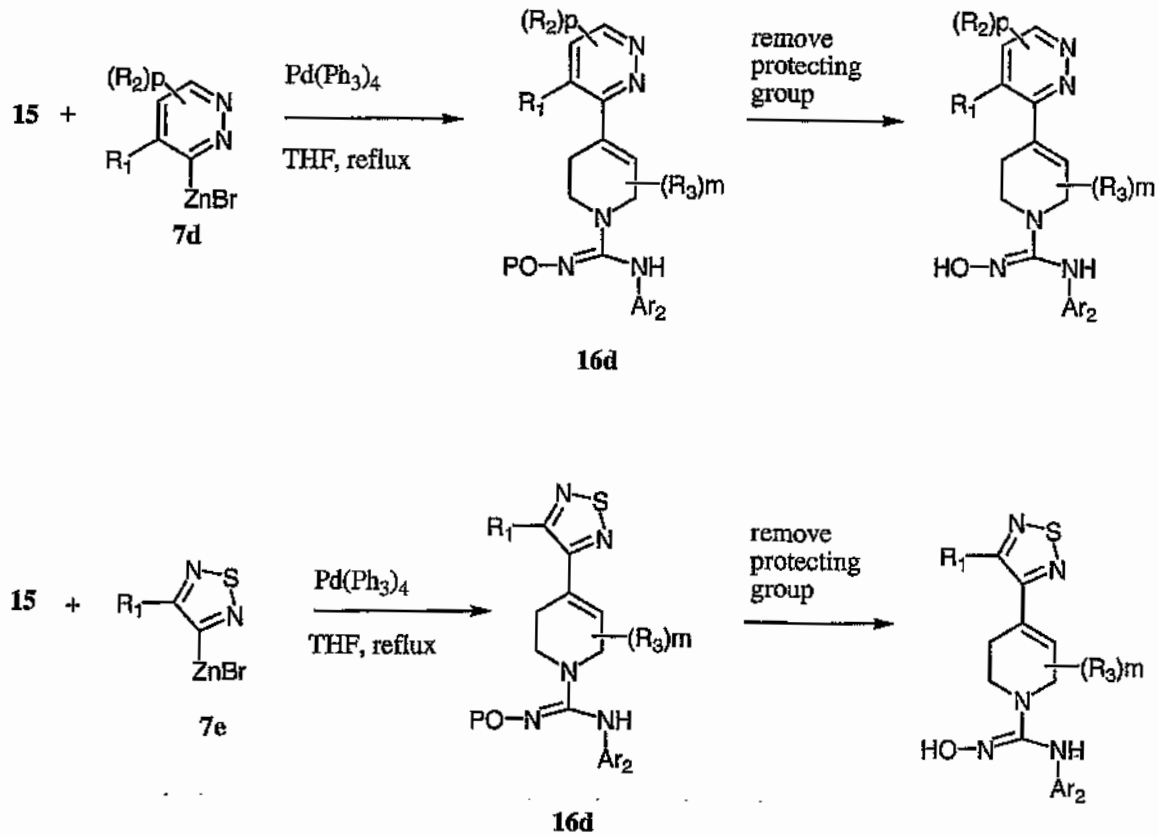


13 **14** **14** **5** **15**


15 +
7a
Pd(Ph3)4
THF, reflux
remove
protecting
group
16a


15 +
7b
Pd(Ph3)4
THF, reflux
remove
protecting
group
16b


15 +
7c
Pd(Ph3)4
THF, reflux
remove
protecting
group
16c

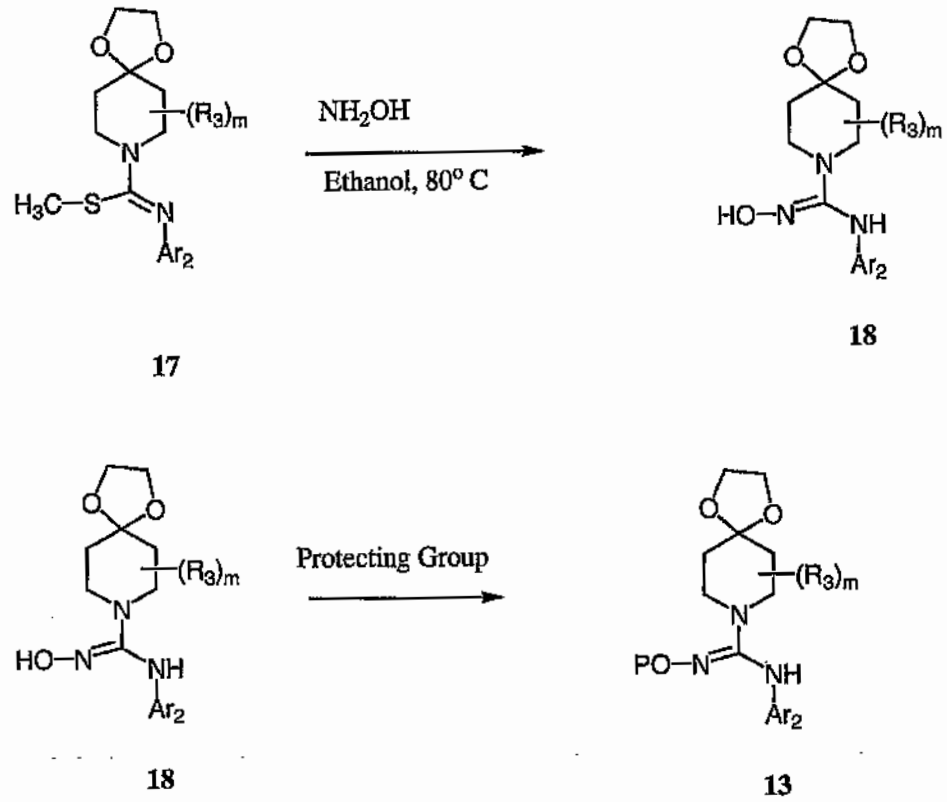


where Ar_2, R_1, R_2, R_3, n, m, and p are defined above for the Tetrahydropiperidyl Compounds and P is a hydroxyl protecting group.

The method for obtaining the Tetrahydropiperidyl Compounds where X is N-OH as described in Scheme **6** is analogous to that described in Schemes **3** and **4** to provide the Tetrahydropiperidyl Compounds where X is N-CN except that a compound of formula **13** is used in place of the compound of formula **9**.

The compound of formula **13** can be obtained as described below in Scheme **7.**

Scheme 7



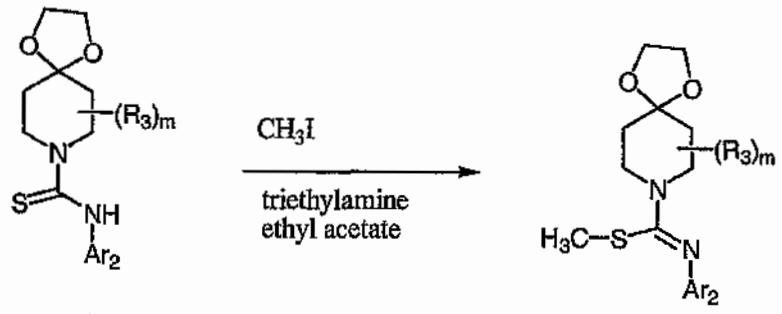
where Ar_2, R_3, and m are defined above for the Tetrahydropiperidyl Compounds and P is a hydroxyl protecting group.

A compound of formula **17** (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 **18**. The hydroxyl group of the compound of formula **18** is then protected using an hydroxyl protecting group to provide the compound of formula **13**. Any hydroxyl protecting group known to those skilled in the art can be used to protect the hydroxyl group in the compound of formula **18**. Suitable hydroxyl protecting groups and methods for their removal are disclosed in T.W. Greene *et al*, *Protective Groups in Organic Synthesis* 17-200 (3d ed. 1999).

Where m = 1, a mixture of Tetrahydropiperidyl compounds is generally obtained. The mixture can be separated via conventional methods, for example, column chromatography.

The compound of formula **17** can be obtained as shown below in Scheme **8.**

Scheme 8



19 **17**

where Ar_2, R_3, and m are defined above for the Tetrahydropiperidyl Compounds.

A solution of a compound of formula **19** (about 0.6 mmol), obtained as described above in section 4.4.2, 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 **17** which can then be purified. In one embodiment, the compound of formula **17** is purified using column chromatography or recrystallization.

4.4.5 Methods for Making the Tetrahydropiperidyl Compounds Where X is N-OR_{10}

The Tetrahydropiperidyl Compounds where X is N-OR_{10} can be obtained by reacting a Tetrahydropiperidyl Compounds where X is N-OH, obtained as described above in Scheme **6**, with X-(C_1-C_4)alkyl, where X is -I, -Br, -Cl, or -F, in the presence of about 3 eq. of triethylamine in THF, with stirring, at about 25°C for about 12 h or at about 50°C for about 3 h. The solvent is then removed from the reaction mixture under reduced pressure to provide a residue. The residue is then purified using silica gel column chromatography eluted with a gradient elution of 100:0 hexane:ethyl acetate to 25:75 hexane:ethyl acetate to provide the Tetrahydropiperidyl Compounds where X is N-OR_{10}. In one embodiment, X is -I or -Br.

Where m = 1, a mixture of Tetrahydropiperidyl Compounds is generally obtained. The mixture can be separated via conventional methods, for example, column chromatography.

Certain Tetrahydropiperidyl Compounds can have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A Tetrahydropiperidyl Compound can be in the form of an optical isomer or a diastereomer. Accordingly, the invention encompasses Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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.

4.5. THERAPEUTIC USES OF THE TETRAHYDROPIPERIDYL COMPOUNDS

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

In one embodiment, an effective amount of a Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl Compounds can be used to treat or prevent acute or chronic pain. Examples of pain treatable or preventable using the Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease 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 disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and artherosclerosis; 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 Tetrahydropiperidyl 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 administered as a treatment for cancer.

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

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

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

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

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

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

The Tetrahydropiperidyl 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*, miliaria, 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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, dementia caused by AIDS, and dementia caused by Alzheimer's disease.

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

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

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

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

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

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

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

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

Applicants believe that the Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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.

4.6 THERAPEUTIC/PROPHYLACTIC ADMINISTRATION AND COMPOSITIONS OF THE INVENTION

Due to their activity, the Tetrahydropiperidyl Compounds are advantageously useful in veterinary and human medicine. As described above, the Tetrahydropiperidyl Compounds are useful for treating or preventing a condition in an animal in need thereof.

When administered to an animal, the Tetrahydropiperidyl Compounds are administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The present compositions, which comprise a Tetrahydropiperidyl Compound, can be administered orally. The Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl Compounds into the bloodstream.

In specific embodiments, it can be desirable to administer the Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl Compounds can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 lidocaine 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 ampule or sachette indicating the quantity of active agent. Where the Tetrahydropiperidyl 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 Tetrahydropiperidyl Compounds are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

The Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Tetrahydropiperidyl Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Tetrahydropiperidyl Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Tetrahydropiperidyl Compound in the body, the Tetrahydropiperidyl Compound can be released from the dosage form at a rate that will replace the amount of Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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.

The Tetrahydropiperidyl 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

Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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-steroidal 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 inhibiting 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-aminophenol 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 Tetrahydropiperidyl Compounds. 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, odansteron, 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 zimelidine.

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, streptozotocin, 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; odansteron; 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; olsalazine; 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, ipsapirone, 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, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, 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, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, 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 odansteron, 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, maprotiline, nefazadone, nortriptyline, protriptyline, trazodone, trimipramine, and venlafaxine; 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 Tetrahydropiperidyl Compound and the other therapeutic agent can act additively or, in one embodiment, synergistically. In one embodiment, a Tetrahydropiperidyl Compound is administered concurrently with another therapeutic agent; for example, a composition comprising an effective amount of a Tetrahydropiperidyl Compound and an effective amount of another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a Tetrahydropiperidyl 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 Tetrahydropiperidyl Compound is administered prior or subsequent to administration of an effective amount of another therapeutic agent. In this embodiment, the Tetrahydropiperidyl Compound is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Tetrahydropiperidyl Compound exerts its therapeutic effect for treating or preventing a Condition.

A composition of the invention is prepared by a method comprising admixing a Tetrahydropiperidyl 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 Tetrahydropiperidyl Compound is present in the composition in an effective amount.

4.7 KITS

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

A typical kit of the invention comprises a unit dosage form of a Tetrahydropiperidyl Compound. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Tetrahydropiperidyl Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Tetrahydropiperidyl 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

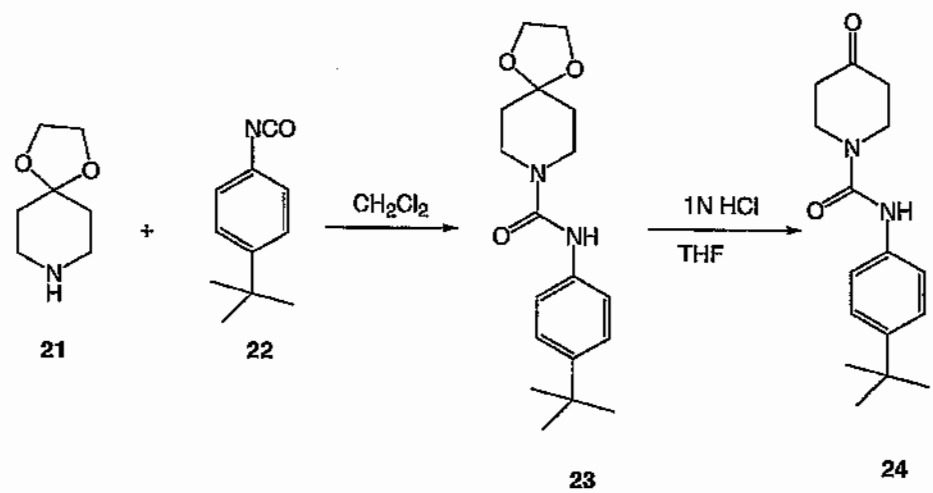
excipient. In another embodiment, the kit comprises a container containing an effective amount of a Tetrahydropiperidyl Compound, an effective amount of another therapeutic agent and a pharmaceutically acceptable carrier or excipient. Examples of other therapeutic agents include, but are not limited to, those listed above.

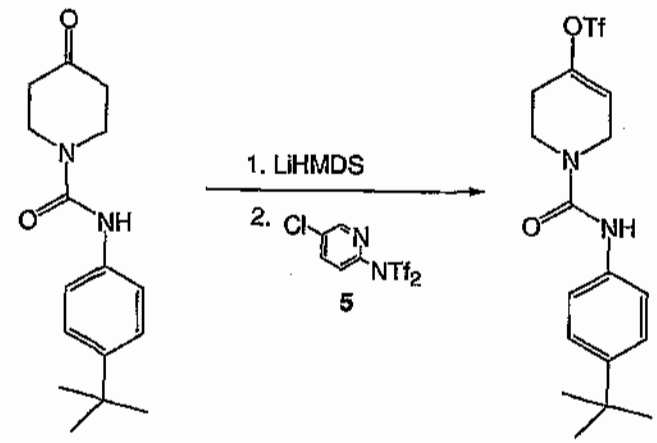
Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device include, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

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.

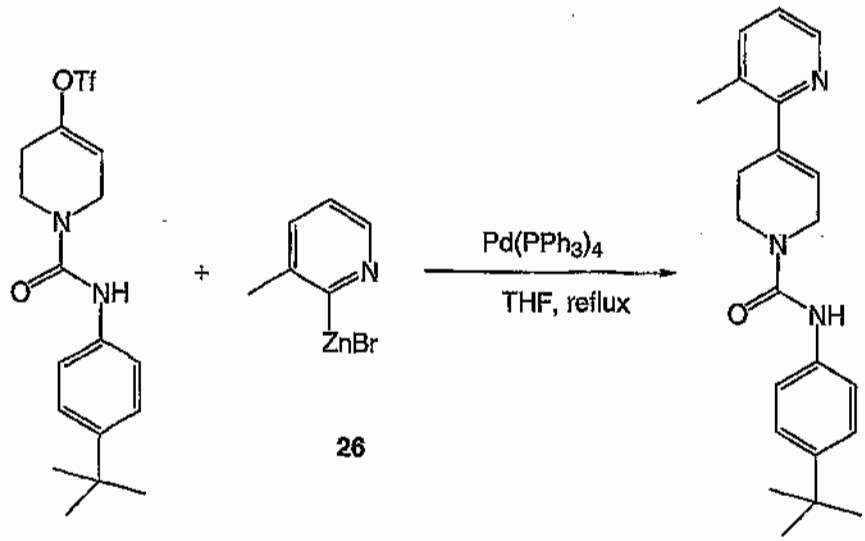
5. EXAMPLES

5.1 EXAMPLE 1: SYNTHESIS OF A TETRAHYDROPIPERIDYL COMPOUND J37(c)





24 25



26

25

J37(c)

A solution of 4-*tert*-butyl phenyl isocyanate **22** (2.45 g, 14 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in DCM (7 mL) was added to a solution of 1,4-dioxa-8-azaspiro[4,5]decane **21** (2g, 14 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in DCM (7 mL) at about 25°C and the resulting reaction mixture was allowed to stir for 5 minutes. The solvent was removed under reduced pressure to provide a compound of formula **23**. The compound of formula **23** was dissolved in THF (20 mL) and 1N HCl in acetic acid (30 mL) was added to the solution. The resulting reaction mixture was then heated at reflux temperature for about 3 h, cooled to about 25°C, and the solvent removed under reduced pressure to provide a residue. The resulting residue was dissolved in DCM, neutralized with saturated aqueous Na_2CO_3 solution, and the organic

layer separated from the aqueous layer. The aqueous layer was then extracted three times with DCM and the DCM layers combined. The combined DCM layers were dried ($MgSO_4$) and the DCM removed under reduced pressure to provide a compound of formula **24**. The compound of formula **24** was purified by column chromatography using a silica gel column eluted with hexane/ethyl acetate (1:1). The compound of formula **24** was obtained as a white solid (1.6 g, 42% yield).

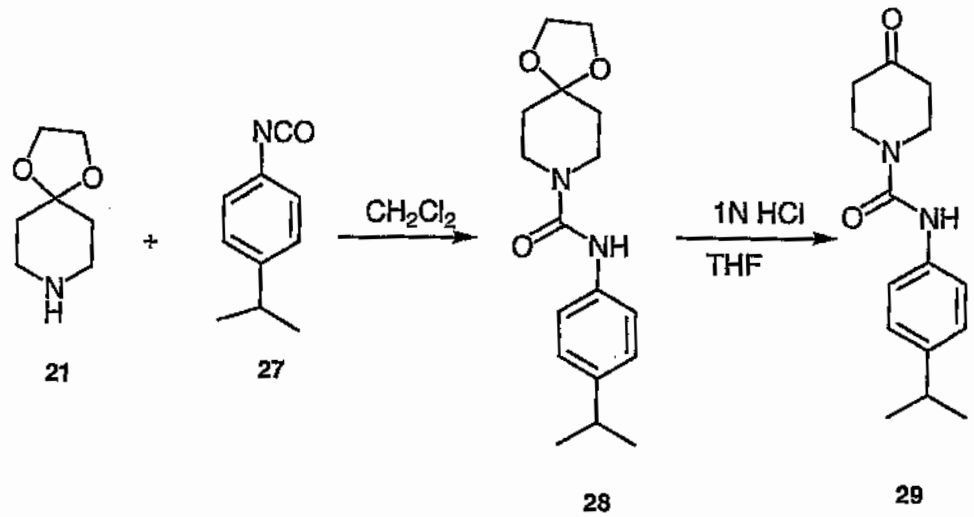
The compound of formula **24** (1 g, 3.64 mmol) was dissolved in THF (100 mL) and the resulting solution cooled to about -78°C. To the cooled solution was then added a 1M solution of LiHMDS in THF (8.75 ml, 8.75 mmol) and the resulting reaction mixture was allowed to stir at about -78°C for about 2 h. After stirring for 2 h, of 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine **5** (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) (1.43 g, 3.64 mmol), dissolved in about 5 mL of THF at -78°C, was added to the reaction mixture and the reaction mixture was allowed to stir at -78 C for another 2 h. The reaction mixture was then allowed to warm to about 25°C and the solvent was removed under reduced pressure to provide a residue. The resulting residue was purified by column chromatography using a silica gel column eluted with hexane/ethyl acetate (5:1) to provide a compound of formula **25** as white solids (0.9 g, 62% yield).

The compound of formula **25**, (0.9 g, 2.21 mmol) and palladium tetrakistriphenylphosphine ($Pd(PPh_3)_4$) (128 mg, 0.111 mmol) were dissolved in THF (50ml) and 0.5 M solution of a compound of 3-methyl-2-pyridylzinc bromide **26** in THF (13.3 ml, 6.64 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was added to the reaction mixture. The reaction mixture was heated at reflux temperature for about 1 h, cooled to about 25°C, and the solvent removed under reduced pressure to provide a residue. The resulting residue was purified by column chromatography using a silica gel column eluted with hexane/ethyl acetate (1:1) to provide Compound **J37(c)**. Compound **J37(c)** was then further purified by trituation with ethyl acetate to provide Compound **J37(c)** as a white solid (490 mg, 63%).

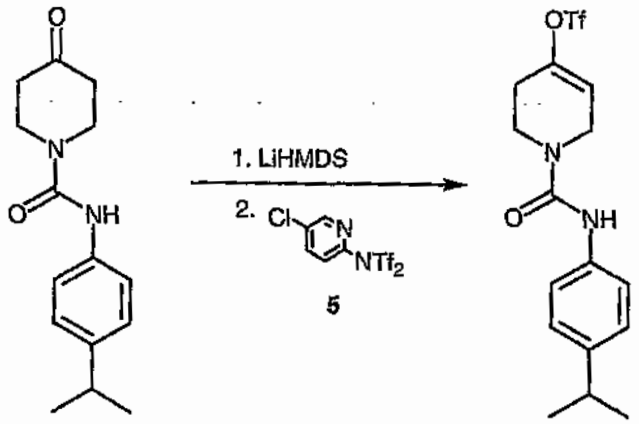
The identity of Compound **J37(c)** was confirmed using ^{1}H-NMR spectroscopy.

Compound **J37(c)**: ^{1}H-NMR ($CDCl_3$): δ 1.31(9H, s), 2.36 (3H, s), 2.64(2H, br), 3.77 (2H, m), 4.19 (2H, m), 5.85 (1H, m), 6.48 (1H, s), 7.13 (1H, m), 7.33(4H, dd), 7.52 (1H, m), 8.44 (1H, m).

5.2 EXAMPLE 2: SYNTHESIS OF A TETRAHYDROPIPERIDYL COMPOUND J39(c)

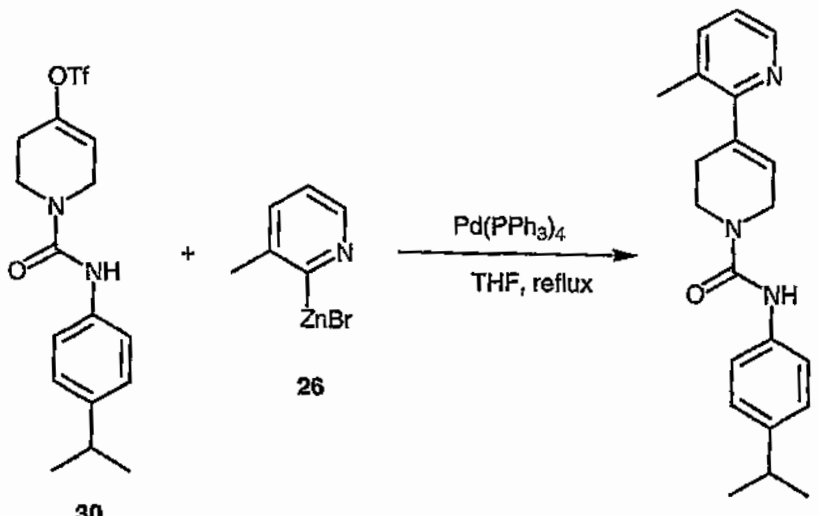


21 27 28 29



5

29 30



26

30 J39(c)

A solution of 4-*iso*-propyl phenyl isocyanate **27** (2.25 g, 14 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in DCM (7 mL) was added to a solution of 1,4-dioxa-8-azaspiro[4,5]decane **21** (2 g, 14 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in DCM (7 mL) at about 25°C and the resulting reaction mixture was allowed to stir for 5 minuets. The solvent was removed under reduced pressure to provide a compound of formula **28**. The compound of formula **28** was dissolved in DCM (30 mL) and trifluoroacetic acid (15 mL) was added to the solution. The resulting reaction mixture was then heated at reflux temperature for about 5 hours, cooled to about 25°C, and the solvent removed under reduced pressure to provide a residue. The resulting residue was dissolved in DCM, neutralized with saturated aqueous Na_2CO_3 solution, and the organic layer separated from the aqueous layer. The aqueous layer was then extracted three times with DCM and the DCM layers combined. The combined DCM layers were dried ($MgSO_4$) and the DCM removed under reduced pressure to provide a compound of formula **29** as a white solid (3.6 g, quantitative yield).

The compound of formula **29** (1.5 g, 5.76 mmol) was dissolved in THF (100 mL) and the resulting solution cooled to about -78°C. To the cooled solution was then added a 1M solution of LiHMDS in THF (13.8 ml, 13.8 mmol) and the resulting reaction mixture was allowed to stir at about -78°C for about 2 hours. After stirring for 2 h, 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine **5** (2.26 g, 5.76 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)), dissolved in about 5 mL of THF at -78°C, was added to the reaction mixture and the reaction mixture was allowed to stir at -78°C for another 2 h. The reaction mixture was then allowed to warm to about 25°C and the solvent was removed under reduced pressure to provide a residue. The resulting residue was purified by flash column chromatography using a silica gel column eluted with an hexane/ethyl acetate gradient (12:1 to 6:1) to provide a compound of formula **30** as yellow oil (0.5 g, 22% yield).

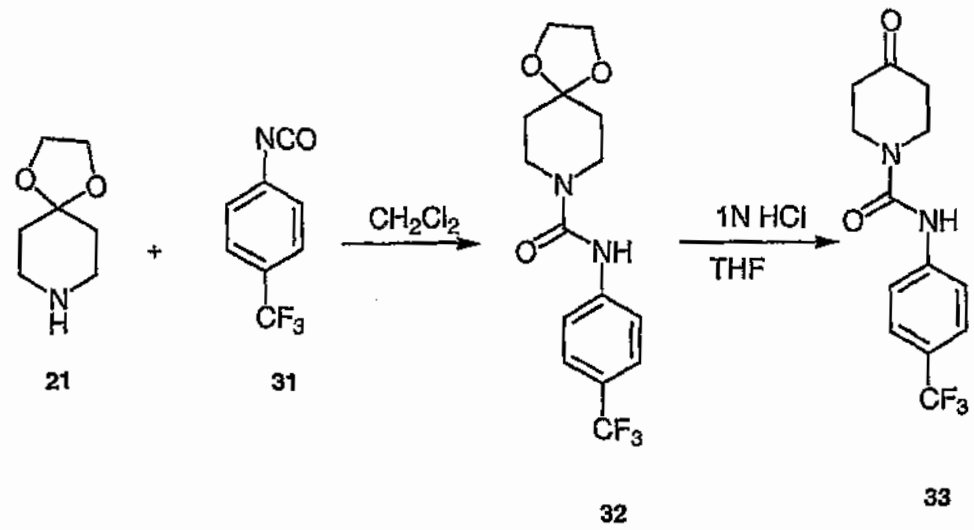
The compound of formula **30**, (0.5 g, 1.25 mmol) and $Pd(PPh_3)_4$ (72.2 mg, 0.063 mmol) were dissolved in THF (20 mL) and 0.5 M solution of 3-methyl-2-pyridylzinc bromide **26** in THF (7.5 ml, 3.75 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was added to the reaction mixture. The reaction mixture was heated at reflux temperature for about 1 h, cooled to about 25°C, and the solvent removed under reduced pressure to provide a residue. The resulting

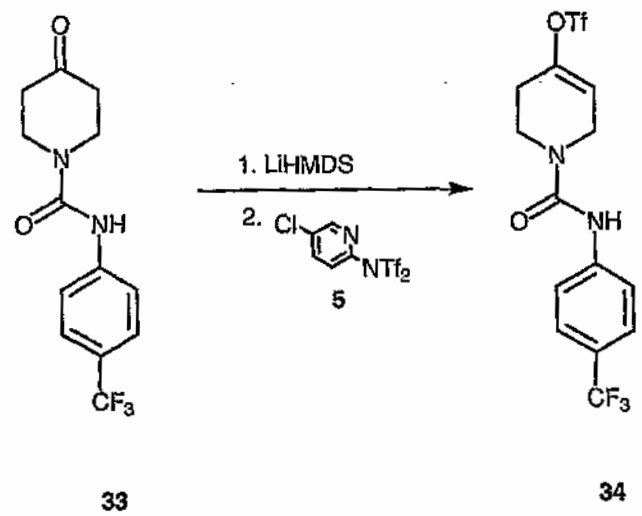
residue was purified by column chromatography using a silica gel column eluted with hexane/ethyl acetate (1:3) to provide Compound **J39(c)**. Compound **J39(c)** was then further purified by trituation with diethylether followed by preparative thin-layer chromatography (silica gel eluted with hexane/ethyl acetate (1:1)) to provide Compound **J39(c)** as a white solid (20 mg, 5%).

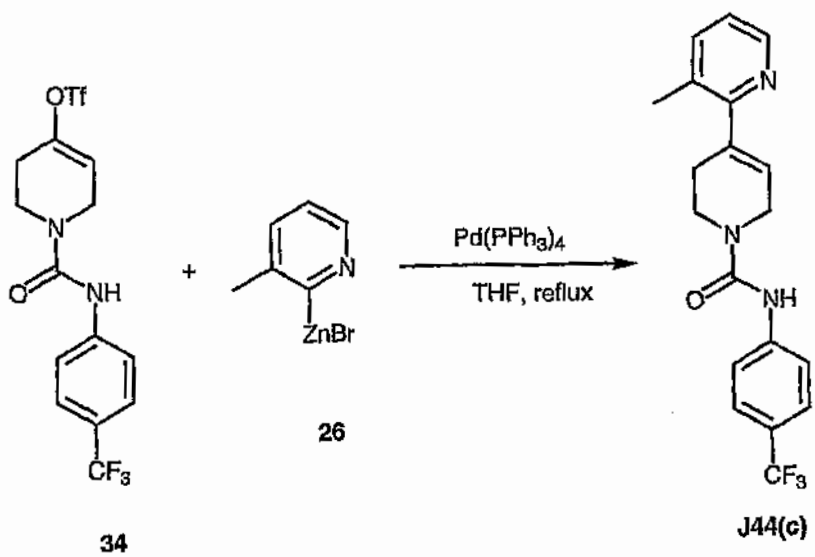
The identity of Compound **J39(c)** was confirmed using ^{1}H-NMR spectroscopy.

Compound **J39(c)**: ^{1}H-NMR ($CDCl_3$): δ 1.25 (6H, d, J=6.7Hz), 2.37 (3H, s), 2.66 (2H, m), 2.89 (1H, m), 3.78 (2H, t, J= 11.2Hz), 4.20 (2H, dd, J= 2.7, 3Hz), 5.86 (1H, m), 6.38 (1H, s), 7.13 (1H, dd, J= 4.9, 7.9Hz), 7.18 (2H, m), 7.32 (2H, m), 7.53 (1H, m), 8.45 (1H, m).

5.3 EXAMPLE 3: SYNTHESIS OF A TETRAHYDROPIPERIDYL COMPOUND J44(c)







A solution of 4-trifluoromethylphenyl isocyanate **31** (6.86 g) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was added in one portion to a solution of 1,4-dioxa-8-azaspiro[4,5]decane **21** (5 g) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in DCM (40 mL) at about 25°C and the resulting reaction mixture was allowed to stir for about 2 h. The solvent was removed under reduced pressure to provide a compound of formula **32**. The compound of formula **32** was dissolved in THF (100 mL) and 2N HCl (100 mL) was added to the solution. The resulting reaction mixture was then heated at about 50 °C for about 4 h and cooled to about 25°C. The aqueous and organic layers were then separated, the aqueous layer was extracted with ethyl acetate (100 mL), and the organic layers were combined. The combined organic layers were then dried ($MgSO_4$) and the solvent removed under reduced pressure to provide a residue. The residue was purified by column chromatography using a silica gel column eluted with hexane/ethyl acetate (1:1) to provide the compound of formula **33** (2.71 g).

The compound of formula **33** (1.03 g) was dissolved in THF (50 mL) and the resulting solution cooled to about -78°C. To the cooled solution was then added a 1M solution of LiHMDS in THF (9 mL) and the resulting reaction mixture was allowed to stir at about -78°C for about 1 hour. After stirring for 1 h., 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine **5** (1.7g,) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in 20 mL of THF was added dropwise to the reaction mixture over a period of about 20 minutes. The solvent was removed under reduced pressure to provide a residue. The resulting residue was purified by column chromatography using a silica gel column eluted with hexane/ethyl acetate (1:1) to provide a compound of formula **34** as white solids (0.9 g).

The compound of formula **34**, (2.3 g) in THF (30 mL) was added in one portion to $Pd(PPh_3)_4$ (318 mg) in THF (70 mL) followed by 3-methyl-2-pyridylzinc bromide **26** (33 ml, 0.5 M in THF) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)). The resulting reaction mixture was heated at reflux temperature for about 3 h, cooled to about 25°C, and the solvent removed under reduced pressure to provide a residue. The residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate (2 x 100 mL) and water (100 mL). The ethyl acetate was then dried (Na_2SO_4) and the solvent removed under reduced pressure to provide a residue. The resulting residue was purified by column chromatography using a

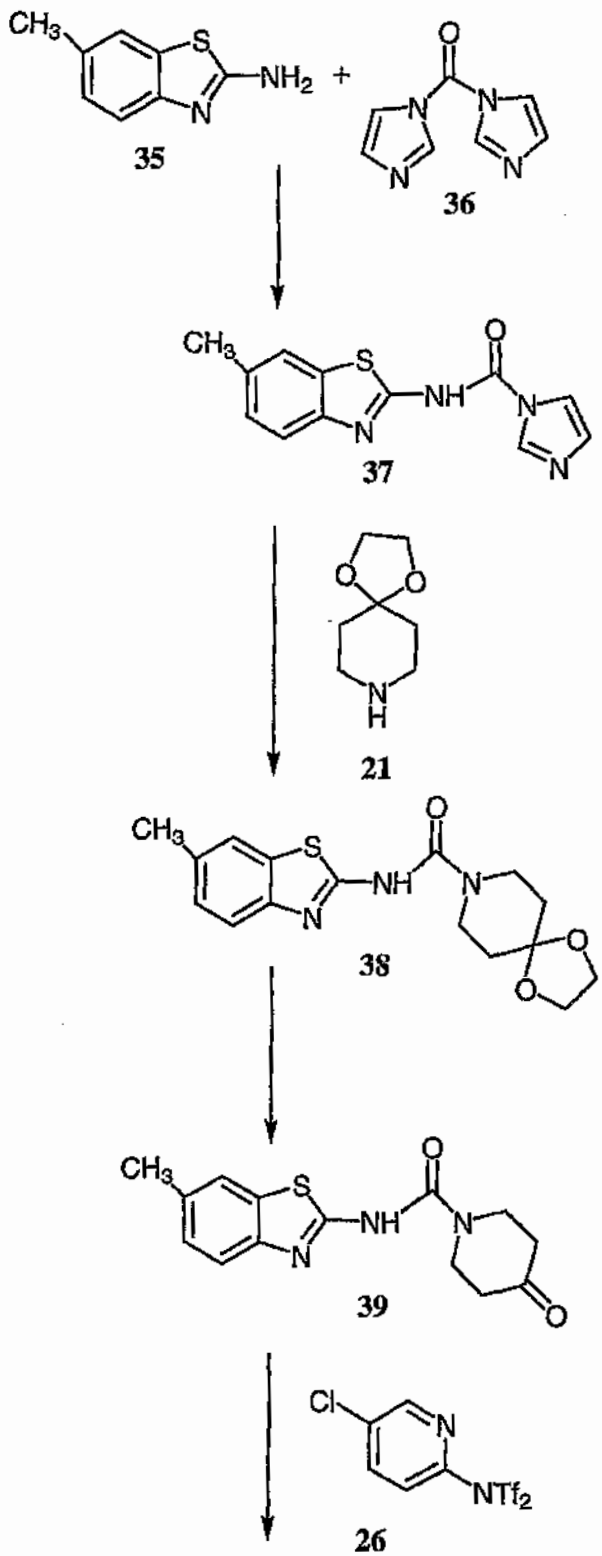
silica gel column eluted with hexane/ethyl acetate (1:2) to provide Compound **J44(c)** (1.8 g).

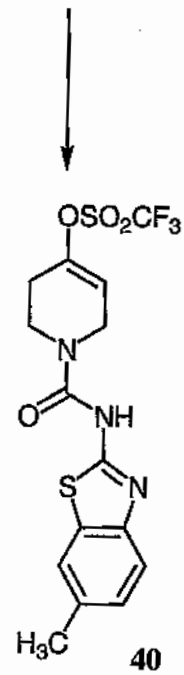
The identity of Compound **J44(c)** was confirmed using ^{1}H-NMR spectroscopy and mass spectrometry.

Compound **J44(c)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (1H, dd, *J*4.7 and 1.1 Hz), 7.57-7.52 (5H, m), 7.13 (1H, dd, *J*7.7 and 4.7 Hz), 6.62 (1H, s), 5.87-5.85 (1H, m), 4.22 (2H, q, *J*2.7 Hz), 3.79 (2H, t, *J*5.6 Hz), 2.68-2.65 (2H, m) and 2.36 (3H, s).

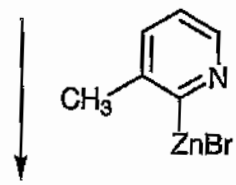
MS (ES+) 362 $(M+H)^+$.

5.4 EXAMPLE 4: SYNTHESIS OF A TETRAHYDROPIPERIDYL COMPOUND I41(c)

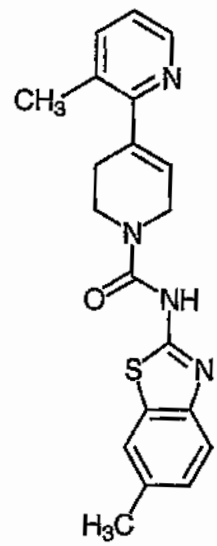




40



26



I41(c)

6-Methyl-2-amino-benzothiazole **35** (10 g, 60.89 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was dissolved in DMF (100 mL) and cooled to about 0°C under a nitrogen atmosphere. To the resulting

solution was added 1,1-carbonyldiimidazole **36** (11.1 g, 66.98 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) and the resulting reaction mixture was stirred for about 1 h at about 0°C. The reaction mixture was then allowed to warm to about 25°C over about 3 hours. The reaction mixture was diluted with acetone (100 mL) and filtered to provide the acyl imidazolide **37** (13.2 g, 84%) as a white solid. The acyl imidazolide **37** was suspended in dry DMF (100 mL) under a nitrogen atmosphere and 1,4-dioxa-8-azaspiro[4.5]decane **21** (7.32 g, 51.1 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was added to the suspension and the resulting reaction mixture heated to about 100°C for about 1 h. The solvent was then removed under reduced pressure to provide a residue. To the resulting residue was added 250 mL of a 1M sodium carbonate solution and the resulting mixture stirred vigorously for about 1 h. After stirring the reaction mixture was filtered to provide a solid that was washed with water (100 mL) and dried under reduced pressure to provide a compound of formula **38** as a white solid (16 g, 79%).

The compound of formula **38** (25.9 g, 77.68 mmol) was suspended in ethyl acetate (200 mL) and a 1:1 mixture of concentrated HCl and ethyl acetate (50 mL) was added to the solution. The resulting reaction mixture was heated at about 60°C for about 1 h. The reaction mixture was then cooled to about 25°C and partitioned between ethyl acetate (600 mL) and 2M potassium carbonate (600 mL). The organic phase was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting solid was purified by column chromatography using a silica gel column eluted with DCM:methanol (50:1) to provide a compound of formula **39** as a white solid (12.4 g, 55%).

The compound of formula **39** (4.00 g, 13.82 mmol) was dissolved in dry THF 1(50 mL) and cooled to about -78°C under an argon atmosphere. A 1 M solution of LiHMDS in THF (34.55 ml, 34.55 mmol) was added via syringe to the resulting solution and the resulting reaction mixture was stirred at about -78°C for about 2 h. After stirring, 2-[N,N-bis)trifluoromethylsulphonyl)amino]-5-chloropyridine **5** (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in THF (25 mL) was added dropwise to the reaction mixture, the reaction mixture was allowed to warm to about 25°C, and was stirred for about 18 h. The solvent was then removed under reduced pressure to provide a residue that was purified by column chromatography using

a silica gel column eluted with ethyl acetate:hexanes (1:4) to provide a compound of formula **40** (4.6 g, 79.0%).

The compound of formula **40** (2.2 g, 5.22 mmol), 3-methyl-pyridin-2-yl zinc bromide **26** (4.4 g, 18.42 mmol), and $Pd(PPh_3)_4$ (0.355 g, 0.307mmol) were dissolved in THF (80 mL) and the resulting reaction mixture was heated at reflux temperature for about 18 h. The reaction mixture was cooled to about 25°C and partitioned between ethyl acetate (300 mL) and saturated brine solution (300 mL). The organic layer was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure to provide a residue. The residue was purified by column chromatography using a silica gel column eluted with ethyl acetate:hexanes (2:3) to provide Compound **I141(c)** as a white solid (1.1 g, 57%).

5.5 EXAMPLE 5: SYNTHESIS OF A TETRAHYDROPIPERIDYL COMPOUND I40(c)

Compound **I40(c)** was obtained by a method analogous to that used to obtain Compound **I41(c)**, as described above in Example 4, except that 6-fluoro-2-amino-benzothiazole was used in place of 6-methyl-2-amino-benzothiazole.

5.6 EXAMPLE 6: BINDING OF TETRAHYDROPIPERIDYL COMPOUNDS TO mGluR5

The following assay can be used to demonstrate that Tetrahydropiperidyl 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 Tetrahydropiperidyl 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.

5.7 EXAMPLE 7: 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 Tetrahydropiperidyl Compound when food is removed for 16 hours before dosing. A control group acts as a comparison to rats treated with a Tetrahydropiperidyl Compound. The control group is administered the carrier for the Tetrahydropiperidyl Compound. The volume of carrier administered to the control group is the same as the volume of carrier and Tetrahydropiperidyl Compound administered to the test group.

Acute Pain: To assess the actions of the Tetrahydropiperidyl 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 Tetrahydropiperidyl 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:

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

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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl

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.

5.8 EXAMPLE 8: 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 Tetrahydropiperidyl 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*.

5.9 EXAMPLE 9: *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 Tetrahydropiperidyl 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), Tetrahydropiperidyl Compound pre-treatment + carrier, carrier pre-treatment + morphine, Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl Compounds pre-treatment on drug self-administration. On test day, rats are pre-treated with a Tetrahydropiperidyl Compound or excipient and then are allowed to self-administer drug as usual. If the Tetrahydropiperidyl Compound blocks the rewarding effects of morphine, rats pre-treated with the Tetrahydropiperidyl

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).

5.10 EXAMPLE 10: 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 Tetrahydropiperidyl 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 Tetrahydropiperidyl 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.

5.11 EXAMPLE 11: BINDING OF TETRAHYDROPIPERIDYL 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 Tetrahydropiperidyl Compounds bind to and modulate the activity of VR1.

Binding of Compound **A19(c)** to VR1: Assay Protocol

Human VR1 Cloning: Human spinal cord RNA (commercially available from Clontech, Palo Alto, CA) was used. Reverse transcription was 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 were 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 VR1 cDNA sequence was obtained by comparison of the human genomic sequence, prior to annotation, to the published rat sequence. Intron sequences were removed and flanking exonic sequences were joined to generate the hypothetical human cDNA. Primers flanking the coding region of human VR1 were designed as follows: forward primer, GAAGATCTTCGCTGGTTGCACACTGGGCCACA; and reverse primer, GAAGATCTTCGGGGACAGTGACGGTTGGATGT.

PCR of VR1 was 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 was 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 was 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 was 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 were performed according to standard protocols. Full-length sequencing confirmed the identity of the human VR1.

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

pH-Based Assay: Two days prior to performing this assay, cells were 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 were 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 were 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 were then transferred to a FLIPR for assay. Compound **A19(c)** was diluted in assay buffer, and 50 mL of the resultant solution were added to the cell plates and the solution monitored for two minutes. The final concentration of Compound **A19(c)** ranged 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) was then added to each well, and the plates were incubated for 1 additional minute. Data were collected over the entire time course and analyzed using Excel and Graph Pad Prism. Compound **A19(c)** when assayed according to this protocol had an IC_{50} of 735 nM.

Capsaicin-based Assay: Two days prior to performing this assay, cells were 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 were 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 were loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final). After one hour, the cells were washed twice with 0.2 mL of wash buffer and resuspended in 0.1 mL of wash buffer. The plates were transferred to a FLIPR for assay. 50 μL of Compound **A19(c)** diluted with assay buffer were added to the cell plates and incubated for 2 min. The final concentration of Compound **A19(c)** ranged from about 50 pM to about 3 μM. Human VR1 was activated by the addition of 50 μL of capsaicin (400 nM), and the plates were incubated for an additional 3 min. Data were collected over the entire time course and analyzed using Excel and GraphPad Prism. Compound **A19(c)** when assayed according to this protocol had an IC_{50} of 19 nM.

The results of the pH-based assay and the capsaicin-based assay demonstrate that Compound **A19(c)**, an illustrative Tetrahydropiperidyl Compound, binds to and modulates the activity of human VR1.

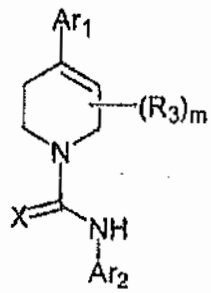
The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the

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.

Claims

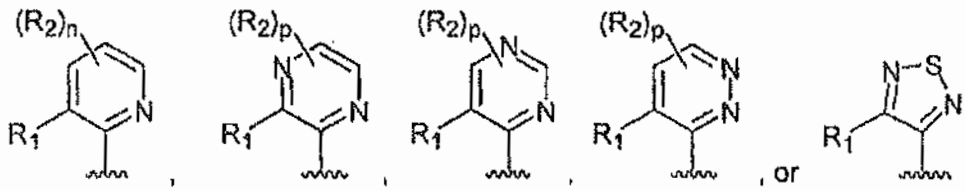
1. A compound of formula:



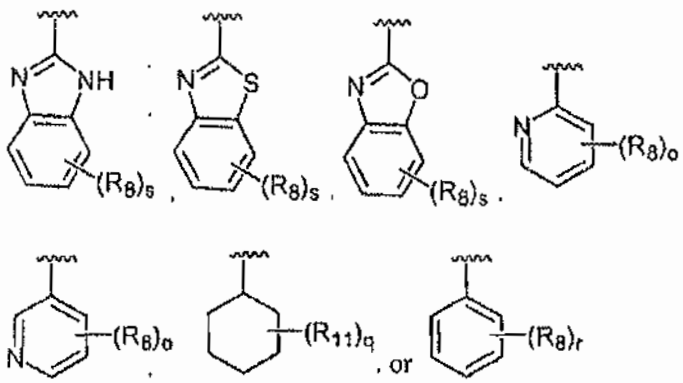
(I)

or a pharmaceutically acceptable salt thereof, wherein

Ar_1 is



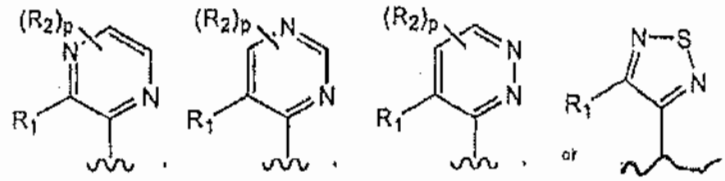
Ar_2 is



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

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

or when Ar_1 is



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, $-NH_2$, -CN, or $-NO_2$;

(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)heterocycle, 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)heterocycle, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_5 is independently -CN, -OH, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

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, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, 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 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, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

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

each R_{11} is independently $-(C_1-C_6)$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, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

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

m is 0 or 1;

o is an integer ranging 0 to 4;

p is an integer ranging from 0 to 2;

n is an integer ranging from 0 to 3;

q is an integer ranging from 0 to 6;

s is an integer ranging from 0 to 4; and

r is an integer ranging from 0 to 5.

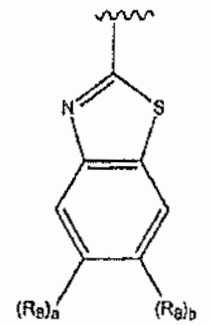
2. The compound of claim 1, wherein X is O, m is 0, p is 0, n is 0 and Ar_1 is a pyridazinyl group or a pyridinyl group.

3. The compound of claim 2, wherein R_1 is -Cl or $-CH_3$.

4. The compound of claim 1 and 2, wherein Ar_2 is a benzothiazolyl group, benzoimidazolyl group, or benzooxazolyl group.

5. The compound of claim 4, wherein s is 0.

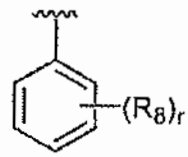
6. The compound of claim 4, wherein Ar_2 is



7. The compound of claim 6, wherein $(R_8)_a$ is -H and $(R_8)_b$ is -$(C_1$-$C_6)$alkyl or -halo.

8. The compound of claim 7, wherein $(R_8)_b$ is an *iso*-propyl group, a *tert*-butyl group or a -halo selected from the group of -F, -Cl, -Br and -I.

9. The compound of claim 3, wherein Ar_2 is



10. The compound of claim 9, wherein r is 1 and R_8 is a -$(C_1$-$C_6)$alkyl.

11. The compound of claim 10, wherein Ar_2 is substituted in the 4-position and -$(C_1$ - $C_6)$alkyl is *tert*-butyl.

12. A composition comprising the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 and a pharmaceutically acceptable carrier or excipient.

13. Use of an effective amount of the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 and optionally an effective amount of another therapeutic agent for the manufacture of a medicament for treating pain in an animal.

14. Use of an effective amount of the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 and optionally an effective amount of another therapeutic agent for the manufacture of a medicament for treating urinary incontinence in an animal.

15. Use of an effective amount of the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 and optionally an effective amount of another therapeutic agent for the manufacture of a medicament for treating an ulcer in an animal.

16. Use of an effective amount of the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 and optionally an effective amount of another therapeutic agent for the manufacture of a medicament for treating irritable-bowel syndrome in an animal.

17. Use of an effective amount of the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 and optionally an effective amount of another therapeutic agent for the manufacture of a medicament for treating inflammatory-bowel disease in an animal.

18. Use of an effective amount of the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 for the manufacture of a medicament for inhibiting VR1 function in a cell.

19. An in-vitro 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 anyone of claims 1 - 9.

20. A kit comprising a container containing an effective amount of the compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9.

21. Method for preparing a composition, comprising the step of admixing a compound or a pharmaceutically acceptable salt of the compound of anyone of claims 1 - 9 and a pharmaceutically acceptable carrier or excipient.