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(54) Title: CALCIUM CHANNEL ANTAGONISTS

(57) Abstract: The present invention provides novel calcium channel antagonists, and methods of treating disease states using the novel antagonists.

CALCIUM CHANNEL ANTAGONISTS

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application claims priority to USSN 60/753,596, filed December 22, 2005 herein incorporated by reference in its entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

Not applicable.

BACKGROUND OF THE INVENTION

[0001] Calcium is an important signaling molecule for many normal physiological processes in the human body. These include electrical signaling in the nervous system, as well as controlling heart and smooth muscle contraction, and hormone release. The entry of calcium into cells is regulated by a diverse set of proteins called calcium channels.

[0002] A fundamental role of Ca²⁺ channels is to translate an electrical signal on the surface membrane into a chemical signal within the cytoplasm, which, in turn, activates many important intracellular processes including contraction, secretion, neurotransmission and regulation of enzymatic activities and gene expression. Tsien et al., (1988), *Trends Neurosci.*, vol. 11, pp. 431-438. Continuing studies have revealed that there are multiple types of Ca²⁺ currents as defined by physiological and pharmacological criteria. See, e. g., Catterall, W.A., (2000) *Annul Rev. Cell Dev. Biol.*, 16:521-55; Llinas et al, (1992) *Trends Neurosci*, 15:351-55; Hess, P. (1990) *Ann. Rev. Neurosci.* 56:337; Bean, B. P. (1989) *Ann. Rev. Physiol.* 51:367-384; and Tsien et al. (1988) *Trends Neurosci.* 11:431-38. In addition to exhibiting distinct kinetic properties, different Ca²⁺ channel types can be localized on different regions of a cell and have complex morphology. The calcium in nerve cells plays an important role in delivering signals between nerve cells. Voltage activated calcium channels play important roles including neuroexcitation, neurotransmission and hormone secretion, and regulation of gene transcription through Ca-dependent transcription factors.

[0003] Voltage dependent calcium channels have been classified by their electrophysiological and pharmacological properties (McCleskey, E. W. et al. *Curr Topics Membr* (1991) 39:295-326, and Dunlap, K. et al. *Trends Neurosci* (1995) 18:89-98). Voltage-gated calcium channels can be divided into Low Voltage Activated calcium channels

(LVA), that are activated at a lower voltage, and High Voltage Activated (HVA) calcium channels, that are activated at a higher voltage with respect to typical resting membrane potentials. HVA channels are currently known to comprise at least three groups of channels, known as L-, N- and P/Q-type channels. These channels have been distinguished from one another electrophysiologically as well as biochemically on the basis of their pharmacology and ligand binding properties. The L-, N-, P/Q-type channels activate at more positive potentials (high voltage activated) and display diverse kinetics and voltage-dependent properties. To date, only one class of low-threshold calcium channels is known, the T-type calcium channels. These channels are so called because they carry a transient current with a low voltage of activation and rapid inactivation. (Ertel and Ertel (1997) *Trends Pharmacol. Sci.* 18:37-42.). In general, T- type calcium channels are involved in the generation of low threshold spikes to produce burst firing (Huguenard, J.R., *Annul Rev. Physiol.*, 329-348, 1996).

[0004] Three genes are known to encode pore forming subunits of T-type calcium channels; CACNA1G (alpha1G, Cav3.1), CACNA1H (alpha1H, Cav3.2), and CACNA1I (alpha1I, Cav3.3) (see Perez-Reyes, *Physiol Rev.* 2003 83:117-61).

[0005] T-type calcium channels are located in the nervous system, cardiac & vascular smooth muscle; as well as a variety of endocrine cell types (see Perez-Reyes, *Physiol Rev.* 2003 83:117-61). Generally, T-type channels are believed to be involved in electrical pacemaker activity, low-threshold calcium spikes, neuronal oscillations and resonance (Perez-Reyes, *Physiol Rev.* 2003 83:117-61). The functional roles for T-type calcium channels in neurons include, membrane depolarization, calcium entry and burst firing. (White et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:6802-6806). Functionally unique calcium channels allow for temporal and spatial control of intracellular calcium and support regulation of cellular activity.

[0006] T-type calcium channels have more negative activation ranges and inactivate more rapidly than other calcium channels. When the range of membrane potentials for activation and inactivation overlap, T-type calcium channels can undergo rapid cycling between open, inactivated, and closed states, giving rise to continuous calcium influx in a range of negative membrane potentials where HVA channels are not normally activated. The membrane depolarizing influence of T-type calcium channel activation can become regenerative and produce calcium action potentials and oscillations.

[0007] In addition to the variety of normal physiological functions mediated by calcium channels, they are also implicated in a number of human disorders. For example, changes to calcium influx into neuronal cells may be implicated in conditions such as epilepsy, stroke, brain trauma, Alzheimer's disease, multiinfarct dementia, other classes of dementia, Korsakoff's disease, neuropathy caused by a viral infection of the brain or spinal cord (e.g., human immunodeficiency viruses, etc.), amyotrophic lateral sclerosis, convulsions, seizures, Huntington's disease, amnesia, pain transmission, cardiac pacemaker activity or damage to the nervous system resulting from reduced oxygen supply, poison or other toxic substances (Goldin et al., US Pat. No. 5,312,928). Other pathological conditions associated with elevated intracellular free calcium levels include muscular dystrophy and hypertension (Steinhardt et al., US Pat. No. 5,559,004).

[0008] Low threshold spikes and rebound burst firing characteristic of T-type calcium currents is prominent in neurons from inferior olive, thalamus, hippocampus, lateral habenular cells, dorsal horn neurons, sensory neurons (DRG, nodose), cholinergic forebrain neurons, hippocampal interneurons, CA1, CA3 dentate gyros pyramidal cells, basal forebrain neurons, amygdala neurons (Talley et al., J. Neurosci., 19: 1895-1911, 1999) and neurons in the thalamus (Suzaki and Rogawski, Proc. Natl. Acad. Sci. USA 86:7228-7232, 1998). As well, T-type channels are prominent in the soma and dendrites of neurons that reveal robust Ca dependent burst firing behaviors such as the thalamic relay neurons and cerebellar Purkinje cells (Huguenard, J.R., Annul Rev. Physiol., 329-348, 1996). Consequently, improper functioning of these T-type calcium channels has been implicated in arrhythmias, chronic peripheral pain, inappropriate pain transmission in the central nervous system.

[0009] The reduction of in vivo hyperalgesic responses to thermal or mechanical stimuli induced by chemical agents (i.e. reducing agents, capsaicin) or experimental nerve injury (i.e. chronic constriction injury; spinal nerve ligation) by known T-type calcium channel antagonists mibefradil and/or ethosuximide suggests a role of the T-type calcium channels in peripheral nerve pain signaling (Todorovic, Neuron, 2001, 31:75-85; Todorovic and Lingle, J. Neurophysiol. 79:240-252, 1998, Flatters SJ, Bennett GJ. Pain. 2004 109:150-61; Dogrul et al; Pain. 2003 105:159-68; Matthews and Dickenson. Eur J Pharmacol. 2001 415:141-9). Furthermore, intrathecal administration of antisense oligonucleotides to alpha1H (Cav3.2) T-type calcium channels in rodents has recently been shown to selectively inhibit the functional expression of T-type calcium currents in sensory neurons and reverse hyperalgesic, and allodynic, responses induced by experimental nerve injury (Bourinet et al EMBO J. 2005

24:315-24). Gene knockout of alpha1G (Cav3.1) T-type channels in mouse CNS is reported to increase the perception of visceral pain (Kim et al. Science. 2003 302:117-9).

[0010] T-type calcium channels promote oscillatory behavior, which has important consequences for epilepsy. The ability of a cell to fire low threshold spikes is critical in the genesis of oscillatory behavior and increased burst firing (groups of action potentials separated by about 50-100 ms). T-type calcium channels are believed to play a vital role in absence epilepsy, a type of generalized non-convulsive seizure. The evidence that voltage-gated calcium currents contribute to the epileptogenic discharge, including seizure maintenance and propagation includes: 1) a specific enhancement of T-type currents in the reticular thalamic (nRT) neurons which are hypothesized to be involved in the genesis of epileptic seizures in a rat genetic model for absence epilepsy (Tsakiridou et al., J. Neurosci., 15: 3110- 3117, 1995); 2) antiepileptics against absence petit mal epilepsy (ethosuximide and dimethadione) have been shown at physiologically relevant doses to partially depress T-type currents in thalamic neurons (Courter et al., Ann. Neurol., 25:582-93, 1989; U.S. 6,358,706 and references cited therein), and; 3) T-type calcium channels underlie the intrinsic bursting properties of particular neurons that are hypothesized to be involved in epilepsy (nRT, thalamic relay and hippocampal pyramidal cells) (Huguenard).

[0011] The T-type calcium channels have been implicated in thalamic oscillations and cortical synchrony, and their involvement has been directly implicated in the generation of cortical spike waves that are thought to underlie absence epilepsy and the onset of sleep (McCormick and Bal, Annul Rev. Neurosci., 20: 185-215, 1997). Oscillations of neural networks are critical in normal brain function such during sleep-wave cycles. It is widely recognized that the thalamus is intimately involved in cortical rhythmogenesis. Thalamic neurons most frequently exhibit tonic firing (regularly spaced spontaneous firing) in awake animals, whereas phasic burst firing is typical of slow-wave sleep and may account for the accompanying spindling in the cortical EEG. The shift to burst firing occurs as a result of activation of a low threshold Ca^{2+} spike which is stimulated by synaptically mediated inhibition (i.e., activated upon hyperpolarization of the RP). The reciprocal connections between pyramidal neurons in deeper layers of the neocortex, cortical relay neurons in the thalamus, and their respective inhibitory interneurons are believed to form the elementary pacemaking circuit.

[0012] Tremor can be controlled through the basal ganglia and the thalamus, regions in which T-type calcium channels are strongly expressed (Talley et al J Neurosci. 1999 19:1895-911). T-type calcium channels have been implicated in the pathophysiology of tremor since the anti-epileptic drug ethosuximide is used for treating tremor, in particular, tremor associated with Parkinson's disease, essential tremor, or cerebellar disease (U.S. Pat. No. 4,981,867; D. A. Prince).

[0013] It is well documented that cortisol is the precursor for glucocorticoids and prolonged exposure to glucocorticoids causes breakdown of peripheral tissue protein, increased glucose production by the liver and mobilization of lipid from the fat depots. Furthermore, individuals suffering from anxiety and stress produce abnormally high levels of glucocorticoids. Consequently, drugs that would regulate these levels would aid in the treatment of stress disorders. In this regard, the observations (Enyeart et al., Mol. Endocrinol., 7:1031-1040, 1993) that T-type channels in adrenal zone fasciculata cells of the adrenal cortex modulate cortisol secretion will greatly aid in the identification of such a therapeutic candidate.

[0014] T-type calcium channels may also be involved sperm production. Sertoli cells secrete a number of proteins including transport proteins, hormones and growth factors, enzymes which regulate germinal cell development and other biological processes related to reproduction (Griswold, Int. Rev. Cytol., 133-156, 1988). While the role of T-type calcium channels remains to be fully elucidated, it is believed that they may be important in the release of nutrients, inhibin B, and/or plasminogen activator and thus may impact sperm production. According to researchers, the inhibition of T-type calcium channels in sperm during gamete interaction inhibits zona pellucida-dependent Ca^{2+} elevations and inhibits acrosome reactions, thus directly linking sperm T-type calcium channels to fertilization.

[0015] In view of the above, pharmacological modulation of T-type calcium channel function is very important and therapeutic moieties capable of modulating T-type currents may find utility in the practice of medicine, i.e., calcium channel blockers for the treatment of pain, epilepsy, hypertension, and angina pectoris etc. Compounds identified thereby may be candidates for use in the treatment of disorders and conditions associated with T-channel activity in humans and animals. Such activities include, but are not limited to, those involving a role in muscle excitability, secretion and pacemaker activity, Ca^{2+} dependent burst firing, neuronal oscillations, and potentiation of synaptic signals, for improving arterial

compliance in systolic hypertension, or improving vascular tone, such as by decreasing vascular welling, in peripheral circulatory disease, and others. Other disorders include, but are not limited to hypertension; cardiovascular disorders (e.g. myocardial infarct, cardiac arrhythmia, heart failure and angina pectoris); neurological disorders (e.g. epilepsy, pain, schizophrenia, depression and sleep); peripheral muscle disorders; respiratory disorders; and endocrine disorders. The present invention meets these and other needs in the art.

BRIEF SUMMARY OF THE INVENTION

[0016] It has been discovered that certain substituted 5-membered nitrogen-containing heteroaryls may be used to antagonize calcium channels.

[0017] In one aspect, the calcium channel antagonist of the present invention is one or all of the compounds set forth in Tables 1-10, Examples 1-36, and/or Table A below.

[0018] In another aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an antagonist of the present invention (e.g. a compound of the present invention or a complex of the present invention).

[0019] In yet another aspect, the present invention provides a method for decreasing ion flow through a voltage-dependant calcium channel in a cell. The method includes contacting the cell with a calcium channel-closing amount of an antagonist of the present invention.

[0020] In still another aspect, the present invention provides a method for treating a disease through antagonizing calcium ion flow through calcium channels.

DETAILED DESCRIPTION OF THE INVENTION

I. ABBREVIATIONS AND DEFINITIONS

[0021] The abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0022] The term "pharmaceutically acceptable salts" is meant to include salts of the active antagonists which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the antagonists described herein. When antagonists of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such antagonists with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium

salt, or a similar salt. When antagonists of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such antagonists with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (*see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977)*). Certain specific antagonists of the present invention contain both basic and acidic functionalities that allow the antagonists to be converted into either base or acid addition salts.

[0023] The neutral forms of the antagonists are preferably regenerated by contacting the salt with a base or acid and isolating the parent antagonist in the conventional manner. The parent form of the antagonist differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0024] In addition to salt forms, the present invention provides antagonists, which are in a prodrug form. Prodrugs of the antagonists described herein are those compounds or complexes that readily undergo chemical changes under physiological conditions, *in vivo*, to provide the antagonists of the present invention. Additionally, prodrugs can be converted to the antagonists of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the antagonists of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0025] Certain antagonists of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain antagonists of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0026] Certain antagonists of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are encompassed within the scope of the present invention.

[0027] The antagonists of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such antagonists. For example, the antagonists may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the antagonists of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0028] The following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
μL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
NaI (sodium iodide);	Hz (Hertz);
MHz (megahertz);	mol (moles);
mmol (millimoles);	RT (ambient temperature);
min (minutes);	h (hours);
mp (melting point);	TLC (thin layer chromatography);
NaOH (sodium hydroxide);	RP (reverse phase);
MeOH (methanol);	<i>i</i> -PrOH (isopropanol);
Et_3N (triethylamine);	TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride);	THF (tetrahydrofuran);
DMSO (dimethylsulfoxide);	EtOAc (ethyl acetate);
DME (1,2-dimethoxyethane);	CH_2Cl_2 (dichloromethane);
POCl_3 (phosphorous oxychloride);	DMF (<i>N,N</i> -dimethylformamide);
CHCl_3 (chloroform);	NaCl (sodium chloride);
Sodium sulfate (Na_2SO_4);	DIEA (<i>N,N</i> -diisopropylethylamine)
HOAc (acetic acid);	Et_2O (diethyl ether);
BOC (<i>tert</i> -butyloxycarbonyl);	Ar (argon);
NH_4OH (Ammonium hydroxide);	CBZ (benzyloxycarbonyl);
Ac (acetyl);	atm (atmosphere);

EtOH (ethanol); NaH (sodium hydride);
 HCl (hydrogen chloride); Me (methyl);
 OMe (methoxy); Et (ethyl);
 Et (ethyl); tBu (tert-butyl);
 LC (liquid chromatography); °C (degrees Centigrade)
 HI (hydrogen iodide); Pd-C (palladium on charcoal)
 LCMS (liquid chromatography couple mass spectrometry)

Unless otherwise noted, the symbols and conventions used herein (processes, schemes and examples) are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*.

II. CALCIUM CHANNEL ANTAGONISTS

[0029] In one aspect, the calcium channel antagonist of the present invention is one or all of the compounds set forth in Tables 1-10, Examples 1-36, and/or Table A below.

Table A

2-(3,4-Dimethoxy-phenyl)-N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-acetamide	2-(3,4-Dimethoxy-phenyl)-N-[5-(4-fluoro-benzenesulfonyl)-thiazol-2-yl]-acetamide
2-(3,4-Dimethoxy-phenyl)-N-[5-(3-trifluoromethoxy-benzenesulfonyl)-thiazol-2-yl]-acetamide	N-(5-Cyclopentylsulfanyl-thiazol-2-yl)-2-(3,4-dimethoxy-phenyl)-acetamide
2-Benzo[1,3]dioxol-5-yl-N-[5-(3-fluoro-benzenesulfonyl)-thiazol-2-yl]-acetamide	[6-(3-Amino-3-methyl-butyl)-2-methyl-pyrimidin-4-yl]-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-amine
2-(4-Chloro-phenyl)-N-[5-(3-methoxy-benzoyl)-thiazol-2-yl]-propionamide	2-(3,4-Dimethoxy-phenyl)-N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-N-methyl-acetamide
(1-Benzyl-piperidin-4-yl)-[5-(4-fluoro-benzenesulfonyl)-thiazol-2-yl]-amine	1-[5-(4-Fluoro-benzenesulfonyl)-thiazol-2-yl]-3-(4-methoxy-benzyl)-urea
5-(4-Fluoro-phenylsulfonyl)-thiazole-2-carboxylic acid 4-methoxy-benzylamide	2-(4-Trifluoromethoxy-phenylsulfanyl)-thiazole-5-carboxylic acid 4-methoxy-benzylamide

[2-(3-Trifluoromethoxy-phenoxy)-thiazol-5-ylmethyl]-(4-trifluoromethyl-benzyl)-amine	3-Phenyl-1-[2-(4-trifluoromethoxy-benzenesulfonyl)-thiazol-5-yl]-propan-1-ol
[2-(3,4-Dimethoxy-phenyl)-ethyl]-[5-(3-ethoxy-phenyl)-thiazol-2-ylmethyl]-carbamic acid tert-butyl ester	3-(3,4-Dimethoxy-phenyl)-1-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-propan-1-one
4-{4-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-pyrimidin-2-yl}-morpholine	N-(2-Amino-2-methyl-propyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-methyl-pyrimidine-4,6-diamine
[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[5-fluoro-2-methyl-6-(2-pyrrolidin-yl-ethoxy)-pyrimidin-4-yl]-amine	(3-{6-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-ylamino]-2-methyl-pyrimidin-4-yl}-1,1-dimethyl-prop-2-ynyl)-carbamic acid tert-butyl ester
[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(3-methoxy-prop-1-ynyl)-2-methyl-pyrimidin-4-yl]-amine	N*2*-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-N*5*-(2-pyrrolidin-1-yl-ethyl)-pyridine-2,5-diamine
[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[2-methyl-6-((R)-pyrrolidin-3-yloxy)-pyrimidin-4-yl]-amine	N-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-methyl-N'(R)-pyrrolidin-3-yl-pyrimidine-4,6-diamine
N-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-N'(R)-pyrrolidin-3-yl-2-trifluoromethyl-pyrimidine-4,6-diamine	N*2*-[5-(4-Fluoro-benzenesulfonyl)-thiazol-2-yl]-N*5*-(2-methoxy-ethyl)-pyridine-2,5-diamine
[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-methoxy-2-morpholin-4-yl-pyrimidin-4-yl]-amine	[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(2-methoxy-ethyl)-2-morpholin-4-yl-pyrimidin-4-yl]-amine
N*5*-[5-(3-Fluoroy-benzenesulfonyl)-thiazol-2-yl]-N*2*-(2-pyrrolidin-1-yl-ethyl)-pyridine-2,5-diamine	

III. ASSAYS FOR BLOCKERS OF VOLTAGE-DEPENDENT T-TYPE CALCIUM CHANNELS

[0030] The activity of T-type calcium channels can be assessed using a variety of in vitro assays, including, but not limited to, measuring changes in cellular cation flux, transmembrane potential, and/or cellular electrical currents. Measurement of ionic fluxes can

be accomplished by measuring changes in the concentration of the permeant species using, for example, calcium sensitive fluorescent dyes (e.g. FLUO-4), or by tracking the movement of small amounts of an appropriately permeant radioactive tracer (e.g. 45-calcium). A preferred means to determine changes in cellular polarization is by measuring changes in current or voltage with the voltage-clamp and patch-clamp techniques, using the "cell-attached" mode, the "inside-out" mode, the "outside-out" mode, the "perforated patch" mode, the "whole cell" mode, or other means of controlling or measuring changes in transmembrane potential (see, e.g., Ackerman et al., *New Engl. J. Med.*, 336: 1575-1595 (1997)). Whole cell currents are conveniently determined using the standard methodology (see, e.g., Hamill et al., *Pflugers. Archiv.* 391: 85 (1981)). Functional consequences of the test compound on ion flux can be quite varied. Accordingly, any suitable physiological change can be used to assess the influence of a test compound on the channels of this invention. For example, the effects of a test compound can be measured by a toxin-binding assay. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as transmitter release, hormone release, transcriptional changes to both known and uncharacterized genetic markers, changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca²⁺, or cyclic nucleotides.

[0031] Antagonists of T-type calcium channels can be tested using recombinant channels, or by examining cells that express native T-type calcium currents (i.e. dorsal ganglion neurons, Todorovic SM, et al (2001) *Neuron.* 31:75-85). Recombinant T-type calcium channels can be transiently or stably expressed in a host cell which can be mammalian in origin (for example, human embryonic kidney (HEK-293) or Chinese Hamster Ovary (CHO) cells) or in other cell systems like amphibian oocytes or insect cells.

[0032] Assays for compounds capable of inhibiting or increasing divalent cation flux through T-type calcium channel proteins can be performed by application of the compounds to a bath solution containing cells expressing functional T-type calcium channels. The compounds are then allowed to contact the cells in the bath. Samples or assays that are treated with a potential T-type calcium channel antagonist are compared to control samples without the test compound, to examine the extent of modulation. Control samples (untreated with inhibitors) are assigned a relative calcium channel activity value of 100. Inhibition of T-type calcium channels is achieved when the calcium channel activity value relative to the control is less than 70%, preferably less than 40%, and still more preferably less than 30% at a concentration of 100 μ M, preferably less than 10 μ M, and still more preferably less than 1

μM . Generally, the compounds to be tested are present in the range from about 1 nM to about 100 mM, preferably from about 1 nM to about 30 μM . In some embodiments, the compounds to be tested are present in the range from about 1 nM to about 3 μM .

IV. PHARMACEUTICAL COMPOSITIONS FOR USE AS POTASSIUM ION CHANNEL ANTAGONISTS

[0033] In another aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an antagonist of the present invention (e.g. a compound of the present invention or a complex of the present invention).

Formulation of the Antagonists

[0034] The antagonists of the present invention can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Thus, the antagonists of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the antagonists described herein can be administered by inhalation, for example, intranasally. Additionally, the antagonists of the present invention can be administered transdermally. Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and either an antagonist, or a pharmaceutically acceptable salt of an antagonist.

[0035] For preparing pharmaceutical compositions from the antagonists of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0036] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0037] The powders and tablets preferably contain from 5% or 10% to 70% of the active antagonist. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar,

lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active antagonist with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0038] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0039] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0040] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0041] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0042] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0043] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

V. METHODS FOR DECREASING ION FLOW IN CALCIUM CHANNELS

[0044] In yet another aspect, the present invention provides a method for decreasing ion flow through a voltage-dependant calcium channel in a cell. The method includes contacting the cell with a calcium channel-closing amount of an antagonist of the present invention.

[0045] In an exemplary embodiment, the voltage-dependent calcium channel is a T- type calcium channel.

VI. METHODS FOR TREATING CONDITIONS MEDIATED BY CALCIUM CHANNELS

[0046] In still another aspect, the present invention provides a method for treating a disease through antagonizing calcium ion flow through calcium channels. An "antagonist," as used herein, means a compound capable of decreasing the flow of ions in a calcium channel relative to the absence of the antagonist.

[0047] The antagonists are useful in the treatment of epilepsy, stroke, anxiety, stress-related disorders, brain trauma, Alzheimer's disease, multi-infarct dementia, Korsakoff's disease, neuropathy caused by a viral infection of the brain or spinal cord, amyotrophic lateral sclerosis, convulsions, seizures, Huntington's disease, amnesia, pain transmission, damage to the nervous system resulting from reduced oxygen supply, poison or other toxic substances, muscular dystrophy, hypertension, cardiac arrhythmia, or low sperm count. This method involves administering, to a patient, an effective amount (e.g. a therapeutically effective amount) of an antagonist of the present invention (a compound or complex of the present invention).

[0048] Thus, the antagonists provided herein find therapeutic utility via antagonism of calcium channels in the treatment of diseases or conditions. In some embodiments, methods include contacting the cell with a calcium channel-closing amount of an antagonist of the present invention. In some embodiments, the calcium channel is a T-type calcium channel.

The cell may be isolated or form part of a organ or organism (e.g. a mammal such as a human).

[0049] In therapeutic use for the treatment of neurological conditions, the antagonists utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.1 mg/kg to about 100 mg/kg is more typical. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the antagonist being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the antagonist. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day.

[0050] The materials and methods of the present invention are further illustrated by the examples which follow, which are offered to illustrate, but not to limit, the claimed invention. The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described, or portions thereof, it being recognized that various modifications are possible within the scope of the invention claimed. Moreover, any one or more features of any embodiment of the invention may be combined with any one or more other features of any other embodiment of the invention, without departing from the scope of the invention. For example, the features of the calcium channel agonists are equally applicable to the methods of treating disease states described herein. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

VII. EXAMPLES

[0051] The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein. All starting materials were obtained from commercial suppliers and used without further purification, unless otherwise noted. Unless otherwise indicated, all reactions conducted under an inert atmosphere at RT. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution. Flash column chromatography was

performed on silica gel (230-400 mesh, Merck) using an ISCO automated system. Melting points were determined using a Mel-Temp II apparatus and are uncorrected.

[0052] ^1H NMR spectra were recorded on a Varian 300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

[0053] Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer SCIEX API-150-EX spectrometer. All mass spectra were taken under electrospray ionization.

Key Intermediate 1 (Int-1A) : 2-bromo-5-(3-ethoxy-benzenesulfonyl)-thiazole

[0054] Part A: A mixture of 3-ethoxythiophenol (10.0 g, 0.065 mol), 2-amino-5-bromothiazole monohydrobromide (17.7 g, 0.068 mol), 1 M aqueous NaOH (200 mL), and THF (200 mL) was stirred at RT for 15 min. The reaction mixture was warmed to 55 °C over 1h, cooled to RT and concentrated under reduced pressure to remove THF. The residue was partitioned between EtOAc (ca. 500 mL) and water (ca 100 mL), and the layers were separated. The organic phase was washed with saturated aqueous NaCl (1 x 200 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a solid. The solid was triturated with CH_2Cl_2 :hexanes (ca. 10:1) to provide 5-(3-ethoxy-phenylsulfanyl)-thiazol-2-ylamine (13.2 g, 80%) as a light brown solid. LCMS (m/z): 253 (M+H)⁺

[0055] Part B: Copper (II) bromide (12.6 g, 57.0 mmol) was added to a mixture of 5-(3-ethoxy-phenylsulfanyl)-thiazol-2-ylamine (13.0 g, 52.0 mol) and acetonitrile (500 mL). The reaction mixture was cooled to 0 °C and *t*-butyl nitrite (9.80 mL, 82.0 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours and was allowed to warm to RT overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 19:1 hexanes:EtOAc), to give 2-bromo-5-(3-ethoxy-phenylsulfanyl)-thiazole (11.4 g, 70%) as an oil.

[0056] Part C: A solution of Oxone® (30.6 g, 0.049 mol) in water (50.0 mL) was added to a solution of 2-bromo-5-(3-ethoxy-phenylsulfanyl)-thiazole (5.25 g, 0.017 mol) in acetone (100 mL) at RT. Saturated aqueous NaHCO_3 was added periodically to maintain pH = 8. The reaction mixture was stirred at RT for 2 h and concentrated under reduced pressure to remove acetone. The aqueous residue was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with saturated aqueous NaCl (1 x 100 mL), dried. The solid was

trituated with hexanes:EtOAc (ca. 19:1) to provide Int-1A (4.40 g, 76%) as a white solid. LCMS (m/z): 348,350 (M+H)⁺

[0057] Using the procedure described above, the following compounds in Table 1 were prepared: Int-1B from 3-(trifluoromethoxy)thiophenol; Int-1C from 3-fluorothiophenol; and Int-1D from 4-fluorothiophenol.

Table 1

Int-1B	2-bromo-5-(3-(trifluoro)methoxy-benzenesulfonyl)-thiazole
Int-1C	2-bromo-5-(4-fluoro-benzenesulfonyl)-thiazole
Int-1D	2-bromo-5-(3-fluoro-benzenesulfonyl)-thiazole

Key Intermediate 2 (Int-2): (6-Chloro-pyrimidin-4-yl)-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]amine

[0058] A mixture of 4-amino-6-chloro-pyrimidine (560 mg, 4.30 mmol) and NaH (60% dispersion in mineral oil, 210 mg, 5.25 mmol) in THF (45 mL) was stirred, under Ar, at 0 °C for 30 min. A solution of Int-1 (1.00 g, 2.90 mmol) in THF (10 mL) was added. The reaction mixture was heated at reflux for 4 h and was allowed to cool to RT. The reaction mixture was quenched with water, acidified with 1N aqueous HCl and partitioned with 10% MeOH/CHCl₃. The organic phase was separated, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 1-100% EtOAc in hexanes, to give Int-2 (566 mg, 50%) as a yellow solid. LCMS (m/z): 397, 399 (M+H)⁺

Key Intermediate 3 (Int-3): (6-Chloro-2-methyl-pyrimidin-4-yl)-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-amine

[0059] Part A: A mixture of 4,6-dichloro-2-methylpyrimidine (1.63 g, 10.0 mmol) in NH₄OH (35%, 8 mL, 200 mmol) was heated, in a Parr bomb, in an oven at 90 °C overnight.

The vessel was cooled to room temperature, the mixture was filtered and the solids were washed with water (3 x 10 mL). Excess solvent was removed *in vacuo* to give 4-amino-6-chloro-2-methylpyrimidine (1.17 g, 81%) as an amorphous solid.

[0060] Part B: A mixture of 4-amino-6-chloro-2-methylpyrimidine (1.54 g, 10.8 mmol) and NaH (60% dispersion in mineral oil, 540 mg, 13.5 mmol) in THF (120 mL) was stirred, under Ar, at 0 °C for 30 min. A solution of Int1-A (2.61 g, 7.49 mmol) in THF (30 mL) was added. The reaction mixture was heated at reflux overnight and was allowed to cool to RT. The reaction mixture was quenched with water, acidified with 1N aqueous HCl and partitioned with 10% MeOH/CHCl₃. The organic phase was separated, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 1-100% EtOAc in hexanes, to give Int-3 (1.80 g, 57%) as a pale yellow solid. LCMS (m/z): 411, 413 (M+H)⁺

Key Intermediate 4 (Int-4): (6-Chloro-5-fluoro-2-methyl-pyrimidin-4-yl)-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-amine

[0061] Part A: A mixture of sodium metal (1.55 g, 67.4 mmol) and EtOH (15.0 mL, 257 mmol) was stirred at RT until nearly all sodium had reacted. Diethyl fluoromalonate (3.54 mL, 22.4 mmol) was added followed by acetamidine hydrochloride (2.14 g, 22.7 mmol). The reaction mixture was heated at reflux for 3 h, cooled to RT and concentrated under reduced pressure. The residue was diluted with water (ca. 50 mL) and acidified (pH = 2) with 6M aqueous HCl, and the mixture was stirred at RT for 1 h as a precipitate formed. The solids were collected by suction filtration and washed with water. Excess solvent was removed *in vacuo* to give 4,6-dihydroxy-5-fluoro-2-methylpyrimidine (2.08 g, 64%) as a light gray solid. LCMS (m/z): 145 (M+H)⁺

[0062] Part B: A mixture of 4,6-dihydroxy-5-fluoro-2-methylpyrimidine (2.00 g, 13.9 mmol), phosphorous oxychloride (15.0 mL, 161 mmol), and *N,N*-dimethylaniline (2.00 mL, 15.8 mmol) was heated at reflux for 2 h. The reaction mixture was cooled to RT and concentrated under reduced press. The residue was poured onto ice and allowed to warm to RT as a ppt formed. The solids were collected by suction filtration, washed with water, and air-dried at RT for 1h to give 4,6-dichloro-5-fluoro-2-methylpyrimidine (1.56 g, 62%) as a tan solid. LCMS (m/z): 181,183 (M+H)⁺

[0063] Part C: A mixture of 4,6-dichloro-5-fluoro-2-methylpyrimidine (1.55 g, 8.56 mmol), ammonium hydroxide (35%, 10.0 mL, 257 mmol), and MeOH (1.00 mL) was heated,

in a sealed tube, at 70 °C for 2h. The reaction mixture was cooled to RT, and a precipitate was formed. The reaction mixture was diluted with water (ca. 10 mL) and was stirred 30 min. The solids were collected by suction filtration, washed with water and air-dried to give 4-amino-6-chloro-5-fluoro-2-methylpyrimidine (845 mg, 61%) as a tan solid. LCMS (m/z): 162,164 (M+H)⁺

[0064] Part D: A mixture of 4-amino-6-chloro-5-fluoro-2-methylpyrimidine (840 mg, 5.20 mmol) and NaH (60% dispersion in mineral oil, 229 mg, 5.73 mmol) in DMF (20.0 mL) was stirred, under Ar, at RT for 15 min. A solution of Int1-A (1.81 g, 5.20 mmol) in DMF (5.0 mL) was added, and the reaction mixture was stirred at RT 15 min. Additional NaH (60% dispersion in mineral oil, 210 mg, 5.25 mmol) was added and the reaction mixture was heated at 60 °C for 30 min. Additional NaH (60% dispersion in mineral oil, 210 mg, 5.25 mmol) was added and the reaction mixture was heated at 60 °C for 1 h. The reaction mixture was cooled to RT and was partitioned between EtOAc (ca. 150 mL) and water (ca. 50 mL). The layers were separated, and the organic layer was washed with saturated aqueous NaCl (1 x 100 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give an oil. The oil was triturated with CH₂Cl₂:hexanes (9:1) to give the Int-4 (1.28 g, 57%) as a pale yellow solid. LCMS (m/z): 429, 431 (M+H)⁺

Key Intermediate 5 (Int-5): (6-Chloro-2-trifluoromethyl-pyrimidin-4-yl)-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-amine

[0065] A mixture of 4-amino-6-chloro-2-trifluoromethyl-pyrimidine [(Inoue, S. et al, *J. Org. Chem.*, 1961, 26, 4504) 185 mg, 0.94 mol] and NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) in DMF (4.0 mL) was stirred, under Ar, at RT for 30 min. A solution of Int1-A (326 mg, 0.94 mmol) in DMF (2.0 mL) was added. The reaction mixture was stirred at RT for 30 min and was heated at 55 °C for 1h. Additional NaH (60% dispersion in mineral oil, 20 mg, 0.05 mmol) was added, and the reaction mixture was heated at 55 °C overnight. Additional NaH (60% dispersion in mineral oil, 20 mg, 0.05 mmol) was added, and the reaction mixture was heated at 55 °C for 1 h. The reaction mixture was cooled to RT and partitioned between EtOAc (ca. 100 mL) and water (ca. 25 mL). The layers were separated and the organic phase was washed with saturated aqueous NaCl (1 x 100 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give an oil. This oil was purified by flash chromatography, elution with 25-75% EtOAc in hexanes, to give Int-5 (182 mg, 42%) as a foam. LCMS (m/z): 465, 467 (M+H)⁺

Key Intermediate 6 (Int-6): [5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-(6-iodo-2-methylpyrimidin-4-yl)-amine

[0066] **Part A:** Hydrogen iodide (3.5 M in water, 30.0 mL) was added to a solution of 4,6-dichloro-2-methylpyrimidine (5.00 g, 0.03 mol) and sodium iodide (23.0 g, 0.15 mol) in acetone (150 mL) at RT for 2 h. The reaction mixture was stirred at RT for 16 h, poured onto ice:water [(ca. 1:1) approx. 250 mL] and allowed to warm to RT. The solids were collected by suction filtration, washed with water, and air-dried to give 4,6-diodo-2-methylpyrimidine (9.80 g, 92%) as an off-white solid. LCMS (m/z): 347 (M+H)⁺

[0067] **Part B:** A suspension of 4,6-diodo-2-methylpyrimidine (1.83 g, 5.29 mmol) in ammonia (2 M solution in EtOH, 10 mL) was heated, in a sealed tube, at 100 °C for 18 h. The reaction mixture was cooled to RT and concentrated under reduced pressure. The solid residue was washed with EtOAc and the filtrate was concentrated under reduced pressure to give 4-amino-6-diodo-2-methylpyrimidine (1.05 g, 84%) as a pale yellow solid. LCMS (m/z): 235 (M+H)⁺

[0068] **Part C:** A mixture of 4-amino-6-diodo-2-methylpyrimidine (500 mg, 2.13 mmol) and NaH (60% dispersion in mineral oil, 170 mg, 4.25 mmol) in DMF (15 mL) was stirred at RT for 30 min. A solution of Int1-A (741 mg, 2.13 mol) in DMF (7 mL) was added, and the reaction mixture was stirred at RT for 1 h. The reaction mixture was poured into EtOAc (ca. 100 mL) and water (ca. 25 mL), 1M aqueous HCl was added to give pH = 7, and the layers were separated. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 40-75% EtOAc in hexanes, to give Int-6 (710 mg, 66%) as an off-white solid. LCMS (m/z): 503 (M+H)⁺

Example 1: 2-(3,4-Dimethoxy-phenyl)-N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-acetamide

[0069] **Part A:** 3-Ethoxythiophenol (0.25 mL, 1.80 mmol) was added to a mixture of 2-(3,4-dimethoxyphenyl)-N-[5-(3-bromothiazol-2-yl)]-acetamide (581 mg, 1.63 mmol), potassium carbonate (340 mg, 2.40 mol) in DMF (8.00 mL). The reaction mixture was heated at 110 °C for 2 hours, was poured onto ice, and was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (2 x 100 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 19:1 hexanes:EtOAc, to give 2-(3,4-Dimethoxyphenyl)-N-[5-(3-ethoxy-

benzenesulfonyl)-thiazol-2-yl]-acetamide (415 mg, 59%) as a pale yellow amorphous solid. LCMS (m/z): 431 (M+H)⁺

[0070] Part B: A solution of Oxone® (2.00 g, 3.00 mmol) in water (8.00 mL) was added to a solution of the compound obtained in **Part A** (415 mg, 0.96 mmol) in acetone (25.0 mL) at RT. Saturated aqueous NaHCO₃ was added periodically to maintain pH = 8. The reaction mixture was stirred at RT over 72 h and concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 1:1 hexanes:EtOAc, to give the title compound (296 mg, 64%) as a white amorphous solid. LCMS (m/z): 463 (M+H)⁺

Example 2

[0071] N-(2-Pyrrolidin-1-ethyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-pyrimidine-4,6-diamine. A mixture of Int-2 (250 mg, 0.63 mmol), N-(2-aminoethyl)pyrrolidine (0.40 mL, 3.0 mmol) and Et₃N (0.19 mL, 1.40 mmol) in 1,4-Dioxane (4 mL) was heated at 90 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 0-20% CMA (CHCl₃:MeOH:NH₄OH; 80:18:2) in CHCl₃ to give the title compound (175 mg, 58%) as an off-white solid. LCMS (m/z): 475 (M+H)⁺

[0072] The procedure described above for Example 2 was used to prepare the compounds below in Table.2:

Table 2

Example 3	N-(2-Dimethylamino-ethyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-pyrimidine-4,6-diamine
Example 4	N-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-N'-(2-methoxy-ethyl)-pyrimidine-4,6-diamine
Example 5	N-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-N'-(2-methoxy-ethyl)-N'-methyl-pyrimidine-4,6-diamine

Example 6

[0073] N-(2-Amino-2-methyl-propyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-methyl-pyrimidine-4,6-diamine.TFA salt. A mixture of Int-3 (600 mg, 1.3 mmol), 1,2-Diamino-2-methylpropane (0.30 mL, 3.0 mmol) and *N,N*-Diisopropylethylamine (0.51 mL, 2.9 mmol) in 1,4-Dioxane (9 mL) was heated, in a sealed tube, at 100 °C overnight. Additional 1,2-diamino-2-methylpropane (0.20 mL, 2.0 mmol) and *N,N*-diisopropylethylamine (0.34 mL, 2.0 mmol) of DIEA were added, and the reaction mixture was heated at 100 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography to give the title compound (574 mg, 70%), as a yellow solid. LCMS (m/z): 463 (M +H)+

[0074] The procedure described above for Example 6 was used to prepare the compounds below in Table 3.:

Table 3

Example 7	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-N'-(2-methoxy-ethyl)-2-methyl-pyrimidine-4,6-diamine
Example 8	N-(2-Dimethylamino-ethyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-methyl-pyrimidine-4,6-diamine
Example 9	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-methyl-N'-(2-pyrrolidin-1-yl-ethyl)-pyrimidine-4,6-diamine

Example 10	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-methyl-N'-(R)-(pyrrolidin-3-yl-ethyl)-pyrimidine-4,6-diamine
Example 11	N-(1-Amino-cyclohexylmethyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-methyl-pyrimidine-4,6-diamine

Example 12

[0075] N-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-5-fluoro-2-methyl-N'-(2-pyrrolidin-1-yl-ethyl)-pyrimidine-4,6-diamine.TFA salt. A mixture of Int-4 (35 mg, 0.08 mmol), N-(2-aminoethyl)pyrrolidine (0.02 mL, 0.20 mmol) and N,N-Diisopropylethylamine (0.03 mL, 0.02 mmol) in DMSO (0.50 mL) was heated at 130 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography to give the title compound (12 mg, 23%) as a white solid. LCMS (m/z): 507 (M +H)+

[0076] The procedure described above for Example 12 was used to prepare the compounds below in Table 4.

Table 4

Example 13	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-5-fluoro-N'-(2-methoxy-ethyl)-2, N'-dimethyl-pyrimidine-4,6-diamine
Example 14	N-(2-Amino-2-methyl-propyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-5-fluoro-2-methyl-pyrimidine-4,6-diamine

Example 15	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-5-fluoro-N'-(2-methoxy-ethyl)-2-methyl-N-(3'-morpholin-4-yl-propyl)-pyrimidine-4,6-diamine
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Example 16

[0077] **N-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-N'-(2-pyrrolidin-1-yl-ethyl)-2-trifluoromethyl-pyrimidine-4,6-diamine.TFA salt.** A mixture of Int-5 (35 mg, 0.08 mmol), N-(2-aminoethyl)pyrrolidine (0.02 mL, 0.20 mmol) and Et₃N (0.02 mL, 0.02 mmol) in 1,4-dioxane (0.50 mL) was heated at 90 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography to give the title compound (27 mg, 55%) as a white solid. LCMS (m/z): 543 (M +H)+

[0078] The procedure described above for Example 16 was used to prepare the compounds below in Table 5.

Table 5

Example 17	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-N'-(2-methoxy-ethyl)-2-trifluoromethyl-pyrimidine-4,6-diamine
Example 18	N-(2-Amino-2-methyl-propyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-trifluoromethyl-pyrimidine-4,6-diamine
Example 19	N-(2-Dimethylamino-ethyl)-N'-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-2-trifluoromethyl-pyrimidine-4,6-diamine

Example 20

[0079] **[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[2-methyl-6-(2-pyrrolidin-1-yl-ethoxy)-pyrimidin-4-yl]-amine – TFA salt.** Sodium hydride (97% dispersion in mineral oil, 370 mg, 15.0 mmol) was added to a solution of *N*- β -hydroxyethylpyrrolidine (850 mg, 7.40 mmol) in DMSO (7 mL) at RT. After 5 min, Added Int-3 (473 mg, 1.15 mmol) was added, and the reaction mixture was heated at 130 °C for 30 min. The reaction mixture was purified directly by reverse phase chromatography, and the product was lyophilized to give the title compd (374 mg, 65%) as a white powder. LCMS (m/z): 490 (M+H)⁺

[0080] The procedure described above for Example 20 was used to prepare the compounds below in Table 6.

Table 6

Example 21	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-[2-methyl-((6R)-1-pyrrolidin-2-yl-methoxy)pyrimidin-4-yl]-amine
Example 22	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-[2-methyl-6-(pyrrolidin-3-yl oxy)pyrimidin-4-yl]-amine
Example 23	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(2-methoxy-ethoxy)-2-methyl-pyrimidin-4-yl]-amine

Example 24

[0081] **[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[5-fluoro-2-methyl-6-(2-pyrrolidin-1-yl-ethoxy)-pyrimidin-4-yl]-amine-TFA salt.** Sodium hydride (97% dispersion in mineral oil, 200 mg, 8.30 mmol) was added to a solution of Int-4 (269 mg, 6.27 mmol) and *N*- β -hydroxyethylpyrrolidine (0.37 mL, 3.20 mmol) in DMSO (3 mL). The reaction mixture was heated at 130 °C for 30 min. The reaction mixture was purified directly by reverse phase chromatography, and the product was lyophilized to give the title compd (118 mg, 35%) as a white powder. LCMS (m/z): 508 (M+H)⁺

[0082] The procedure described above for Example 24 was used to prepare the compounds below in Table 7.

Table 7

Example 25	N-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-[5-fluoro-6-(2-methoxy-ethoxy)-2-methyl-pyrimidin-4-yl]-amine
Example 26	[6-(2-Cyclopentyl-ethoxy)-5-fluoro-2-methyl-pyrimidin-4-yl]-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-amine
Example 27	[6-(2-Dimethylamino-ethoxy)-5-fluoro-2-methyl-pyrimidin-4-yl]-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2-yl]-amine

Example 28

[0083] **[6-(2-Dimethylamino-ethoxy)-2-trifluoromethyl-pyrimidin-4-yl]-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-amine-TFA salt.** Sodium hydride (97% dispersion in mineral oil, 32 mg, 1.3 mmol) was added to a solution of Int-5 (61 mg, 0.13 mmol) and *N,N*-dimethylaminoethanol (0.07 mL, 0.70 mmol) in DMSO (1 mL). The reaction mixture was heated at 130 °C for 30 min. The reaction mixture was purified directly by reverse phase chromatography, and the product was lyophilized to give the title compd (6 mg, 8%) as a tan powder. LCMS (m/z): 518 (M+H)⁺

Example 29

[0084] **[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(3-methoxy-prop-1-ynyl)-2-methyl-pyrimidin-4-yl]-amine.** Copper (I) iodide (2.0 mg, 0.01 mmol) was added to a solution of Int-6 (100 mg, 0.20 mol), methyl propargyl ether (0.02 mL, 0.024 mmol), and Et₃N (0.40 mL, 2.9 mmol) in acetonitrile (2.0 mL) under Ar. Bis(triphenylphosphine)palladium(II) chloride (7.0 mg, 0.01 mol) was added, and the reaction mixture was stirred at RT for 18 h. The reaction mixture was filtered thru Celite

using EtOAc (ca. 50 mL), and the filtrate was concentrated under reduced pressure to give an oil. This oil was purified by flash chromatography, elution with 45-90% EtOAc in hexanes, to give the title compound (41 mg, 46%) of as an off-white solid. LCMS (m/z): 445 (M+H)⁺

[0085] The procedure described above for Example 29 was used to prepare the compounds below in Table 8.

Table 8

Example 30	(3-{6-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-ylamino]-2-methyl-pyrimidin-4-yl}-prop-2-ynyl)-methyl-carbamic acid tert-butyl ester
Example 31	(3-{6-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-ylamino]-2-methyl-pyrimidin-4-yl}-1,1-dimethyl-prop-2-ynyl)-methyl-carbamic acid tert-butyl ester

Example 32

[0086] **[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(3-methoxy-propyl)-2-methyl-pyrimidin-4-yl]-amine.** A mixture of [5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(3-methoxy-prop-1-ynyl)-2-methyl-pyrimidin-4-yl]-amine (32.0 mg, 0.072 mol) and Pd-C (10%, 2.0 mg) in THF (1.00 mL) and EtOAc (1.00 mL) was stirred under H₂ (70 psi, Parr) for 30 min. The reaction mixture was filtered through Celite using EtOAc (ca. 50 mL). The filtrate concentrated under reduced pressure to give the title compound (30 mg, 93%) as an off-white solid. LCMS (m/z): 449 (M+H)⁺

[0087] The procedure described above for Example 32 was used to prepare the compounds below in Table 9.

Table 9

Example 33	(3-{6-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-ylamino]-2-methyl-pyrimidin-4-yl}-propyl)-methyl-carbamic acid tert-butyl ester
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Example 34	(3-{6-[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-ylamino]-2-methyl-pyrimidin-4-yl}-1,1-dimethyl-propyl)-carbamic acid tert-butyl ester
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Example 35

[0088] **[5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(3-methylamino)propyl]-2-methyl-pyrimidin-4-yl]-amine-HCl salt.** A mixture of [5-(3-Ethoxy-benzenesulfonyl)-thiazol-2-yl]-[6-(3-(BOC-amino)lpropyl)-2-methyl-pyrimidin-4-yl]-amine (32.0 mg, 0.058 mol) and HCl (4 Molar solution in 1,4-dioxane, 2.0 mL) was stirred) for 2 h. The reaction mixture was concentrated under reduced pressure to give the title compound (27 mg, 95%) as an off-white solid. LCMS (m/z): 485 (M+H)⁺

[0089] The procedure described above for Example 35 was used to prepare the compounds below in table 10.

Table 10

Example 36	[6-(3-Amino-3-methyl-butyl)-2-methyl-pyrimidin-4-yl]-[5-(3-ethoxy-benzenesulfonyl)-thiazol-2yl]-amine
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Activity Assay

[0090] T-type calcium channel inhibitory activity of some compounds of the invention was evaluated using both fluorometric as well as electrophysiological measurement methodologies, which are known to those skilled in the art.

[0091] Fluorescence measurement of changes in intracellular calcium due to entry of calcium through T-type calcium channels was assessed using calcium sensitive fluorescent dyes Fluo-4 and Fluo-3. In brief, cells natively expressing T-type channels or HEK-293 cells transiently or stably expressing recombinant mammalian T-type calcium channels grown in 96-well tissue culture plates in DMEM/High glucose, Hyclone, Fetal Bovine Serum (10%), and 2 mM sodium pyruvate 2 mM (and for cells lines recombinantly expressing T-type calcium channels, G418 @ 400 mg/liter) were loaded with 4 μM Fluo-4 made up in Earls Balanced Salt Solution (EBSS). After incubation for 30 minutes at room temperature, cells

were washed with low calcium (0.5 mM) EBSS to remove extracellular Fluo-4. Baseline fluorescence was measured in a FLIPR (FLUorescence Image Plate Reader) (Molecular Devices Inc) after applying test compounds at desired concentration for 5-10 minutes. The effect of test compound on calcium entry was assessed by monitoring changes in Fluo-4 fluorescence following an elevation of extracellular calcium concentration from 0.5 mM to 5 mM.

[0092] Electrophysiological measurements of test compound induced changes in T-type calcium channel activity were assessed as follows. Native cells natively expressing T-type channels or HEK-293 cells transiently or stably expressing recombinant mammalian T-type calcium channels were grown in DMEM/High glucose, Hyclone, Fetal Bovine Serum (10%), 2 mM sodium pyruvate 2 mM (and for cells lines recombinantly expressing T-type calcium channels, G418 @ 400 mg/liter) on glass coverslips in 35 mm tissue culture dishes. Experiments were performed by placing T-type calcium channels expressing cells in a recording chamber perfused with EBSS (which contains (in mM): 132 NaCl, 5.4 KCl, 1.8 CaCl₂, 0.8 MgCl₂, 10 Hepes, 5 glucose, pH 7.4 with NaOH) on the stage of an inverted microscope. Electrical currents were measured using the whole cell configuration of the patch clamp technique (Axopatch 200B, Axon Instruments (Molecular Devices) (see Hamill et al (1981) Pflugers Arch. 1981 391:85-100) using 2 – 2.5 MOhm resistance glass pipettes filled with 135 CsF, 5 CsCl, 5 NaCl, 5 EGTA, 10 HEPES, pH 7.3 with CsOH, Osmolarity ~ 288 mOsm. Test compound effects were typically assessed under conditions in which approximately half of the available channels were inactivated either by an 8 second conditioning depolarization from a holding potential of -100 mV to a potential ranging from -70 mV to -60 mV or by continually holding the membrane potential at -70 mV. Test compounds were assessed for their ability to reduce the amplitude of the inward T-type calcium current elicited by a 100 ms step depolarization -20 or -30 mV.

[0093] Results are presented in Table 11 below.

Table 11

Example	Activity
1	+++
2	+++
3	+++
4	++
5	++
6	+++

7	++
8	+++
9	+++
10	+++
11	+++
12	+++
13	+++
14	+++
15	+++
16	+++
17	+++
18	+++
19	+++
20	+++
21	+++
22	+++
23	+++
24	+++
25	+++
26	+
27	+++
28	+++
29	++
30	+++
31	+++
32	+++
35	+++
36	+++

Activity refers to inhibition of T-type calcium channels, where "+" is $10 \mu\text{M} < \text{IC}_{50} \leq 1 \text{ mM}$; "++" is $1 \mu\text{M} < \text{IC}_{50} < 10 \mu\text{M}$; and "+++ is $1 \text{ nM} < \text{IC}_{50} < 1 \mu\text{M}$.

WHAT IS CLAIMED IS:

- 1 1. A compound selected from the compounds set forth in Tables 1-10,
2 Examples 1-36, and/or Table A.
- 1 2. A method of decreasing ion flow through voltage-dependent calcium
2 channels in a cell, said method comprising contacting said cell with a calcium channel-
3 closing amount of a compound of claim 1.
- 1 3. The method of claim 2, wherein said voltage-dependent calcium
2 channel is a T- type calcium channel.
- 1 4. A method of treating a disorder or condition through modulation of a
2 voltage-dependent calcium channel, said method comprising administering to a subject in
3 need of such treatment, an effective amount of a compound of claim 1.
- 1 5. The method of claim 4, wherein said disorder or condition is epilepsy,
2 stroke, anxiety, stress-related disorders, brain trauma, Alzheimer's disease, multi-infarct
3 dementia, Korsakoff's disease, neuropathy caused by a viral infection of the brain or spinal
4 cord, amyotrophic lateral sclerosis, convulsions, seizures, Huntington's disease, amnesia, pain
5 transmission, damage to the nervous system resulting from reduced oxygen supply, poison or
6 other toxic substances, muscular dystrophy, hypertension, cardiac arrhythmia, or low sperm
7 count.
- 1 6. A composition comprising a pharmaceutically acceptable excipient and
2 a compound of claim 1.