REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

FORM P.8
(to be lodged in duplicate)

A&A Ref: **154508**

PUBLICATION PARTICULARS AND ABSTRACT
(Section 32(3)(a) - Regulations 22(1)(g) and 31)

21	01	PATENT APPLICATION NO	22	LODGING DATE	43	ACCEPTANCE DATE
		2006/02684		31 March 2006		~~22~~ 05-01-2007

51	INTERNATIONAL CLASSIFICATION	NOT FOR PUBLICATION

C07D CLASSIFIED BY: **ISA**

71	FULL NAME(S) OF APPLICANT(S)

Neuromed Pharmaceuticals Ltd.

72	FULL NAME(S) OF INVENTOR(S)

SNUTCH, Terrance P.
PAJOUHESH, Hassan
BELARDETTI, Francesco
ZAMPONI, Gerald W.
PAJOUHESH, Hossein

EARLIEST PRIORITY CLAIMED	COUNTRY		NUMBER		DATE	
	33	US	31	10/655,393	32	3 September 2003

NOTE: The country must be indicated by its International Abbreviation - see schedule 4 of the Regulations

54	TITLE OF INVENTION

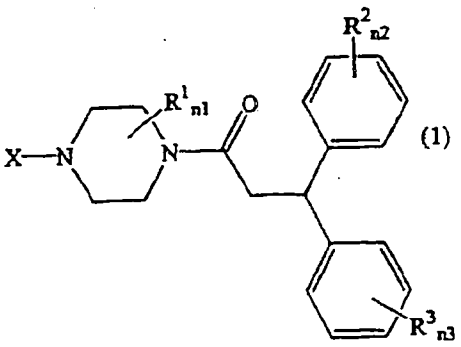
Piperazine substituted compounds used as calcium channel blockers

57	ABSTRACT (NOT MORE THAN 150 WORDS)

NUMBER OF SHEETS	79

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.



(1)

(57) Abstract: New piperazine substituted compounds of formula (1) have been found to be useful in treatinf conditions associated with calcium channel function. These piperazine derivatives are useful in treating conditions such as stroke, pain, anxiety disorders, depression, addiction, gastrointestinal disorders, genitourinary disorders, cardiovascular disease, epilepsy, diabetes and cancer.

PREFERENTIALLY SUBSTITUTED CALCIUM CHANNEL BLOCKERS

Cross-Reference to Related Applications

[0001] This application is a continuation-in-part of U.S. Serial No. 10/655,393, which is a continuation-in-part of U.S. Serial No. 10/060,900 filed 29 January 2002, which is a continuation of U.S. Serial No. 09/476,927 filed 30 December 1999, now U.S. patent 6,387,897. The contents of these applications are incorporated herein by reference.

Technical Field

[0002] The invention relates to compounds useful in treating conditions associated with abnormal calcium channel function. More specifically, the invention concerns compounds containing substituted or unsubstituted derivatives of 6-membered heterocyclic moieties that are useful in treatment of conditions such as stroke and pain.

Background Art

[0003] The entry of calcium into cells through voltage-gated calcium channels mediates a wide variety of cellular and physiological responses, including excitation-contraction coupling, hormone secretion and gene expression (Miller, 1987; Augustine, *et al.*, 1987). In neurons, calcium channels directly affect membrane potential and contribute to electrical properties such as excitability, repetitive firing patterns and pacemaker activity. Calcium entry further affects neuronal functions by directly regulating calcium-dependent ion channels and modulating the activity of calcium-dependent enzymes such as protein kinase C and calmodulin-dependent protein kinase II. An increase in calcium concentration at the presynaptic nerve terminal triggers the release of neurotransmitter and calcium channels, which also affects neurite outgrowth and growth cone migration in developing neurons.

[0004] Calcium channels mediate a variety of normal physiological functions, and are also implicated in a number of human disorders. Examples of calcium-mediated human disorders include but are not limited to congenital migraine, cerebellar ataxia, angina, epilepsy, hypertension, ischemia, and some arrhythmias. The clinical treatment of some of these disorders has been aided by the development of therapeutic calcium channel antagonists (*e.g.*, dihydropyridines, phenylalkyl amines, and benzothiazapines all target L-type calcium channels) (Janis and Triggle, 1991).

[0005] Native calcium channels have been classified by their electrophysiological and pharmacological properties into T-, L-, N-, P/ Q- and R- types (reviewed in Catterall (2000); Huguenard (1996)). T-type (or low voltage-activated) channels describe a broad class of molecules that transiently activate at negative potentials and are highly sensitive to changes in resting potential.

[0006] The L-, N- and P/Q-type channels activate at more positive potentials (high voltage-activated) and display diverse kinetics and voltage-dependent properties (Catterall (2000); Huguenard (1996)). L-type channels can be distinguished by their sensitivity to several classes of small organic molecules used therapeutically, including dihydropyridines (DHP's), phenylalkylamines and benzothiazepines. In contrast, N-type and P/Q-type channels are high affinity targets for certain peptide toxins produced by venous spiders and marine snails: N-type channels are blocked by the ω-conopeptides ω-conotoxin GVIA (ω–CTx-GVIA) isolated from *Conus geographus* and ω-conotoxin MVIIA (ω–CTx-MVIIA) isolated from *Conus magus*, while P/Q-type channels are resistant to ω–CTx-MVIIA but are sensitive to the funnel web spider peptide, ω-agatoxin IVA (ω–Aga-IVA). R-type calcium channels are sensitive to block by the tarantula toxin, SNX-482.

[0007] Neuronal high voltage-activated calcium channels are composed of a large (>200 kDa) pore-forming α_1 subunit that is the target of identified pharmacological agents, a cytoplasmically localized ~ 50-70 kDa β subunit that tightly binds the α_1 subunit and modulates channel biophysical properties, and an ~ 170 kDa $\alpha_2\delta$ subunit (reviewed by Stea, *et al.* (1994); Catterall (2000)). At the molecular level, nine different α_1 subunit genes expressed in the nervous system have been identified and shown to encode all of the major classes of native calcium currents (Table 1).

Table 1

Classification of Neuronal Calcium Channels

Native Class	cDNA	Gene Name	ω-AGA IVA	ω-CTx GVIA	ω-CTx MVIA	dihydropyridines
P/Q-type	α_{1A}	Cav2.1	✓	-	-	-
N-type	α_{1B}	Cav2.2	-	✓	✓	-
L-type	α_{1C}	Cav1.2	-	-	-	✓
L-type	α_{1D}	Cav1.3	-	-	-	✓
R-type	α_{1E}	Cav2.3	-	-	-	-
L-type	α_{1F}	Cav1.4	-	-	-	✓
T-type	α_{1G}	Cav3.1	-	-	-	-
T-type	α_{1H}	Cav3.2	-	-	-	-
T-type	α_{1I}	Cav3.3	-	-	-	-

[0008] Calcium channels have been shown to mediate the development and maintenance of the neuronal sensitization processes associated with neuropathic pain, and provide attractive targets for the development of analgesic drugs (reviewed in Vanegas and Schaible (2000)). All of the high threshold Ca channel types are expressed in the spinal cord, and the contributions of L , N and P/Q types in acute nociception are currently being investigated. In contrast, examination of the functional roles of these channels in more chronic pain conditions strongly indicates a pathophysiological role for the N type channel (reviewed in Vanegas & Schaible (2000)).

[0009] Mutations in calcium channel α_1 subunit genes in animals can provide important clues to potential therapeutic targets for pain intervention. Genetically altered mice null for the α_{1B} N type calcium channel gene have been reported by several independent groups (Ino, et al. (2001); Kim, et al. (2001); Saegusa, et al. (2001); Hatakeyama, et al. (2001)). The α_{1B} N type null mice were viable, fertile and showed normal motor coordination. In one study, peripheral body temperature, blood pressure and heart rate in the N type gene knock out mice were all normal (Saegusa, et al. (2001)). In another study, the baroreflex mediated by the sympathetic nervous system was reduced after bilateral carotid occlusion (Ino, et al. (2001)). In another study, mice were examined for other behavioral changes and were found to be normal except for exhibiting significantly lower anxiety related behaviors (Saegusa, et al. (2001)), suggesting the N type channel may be a potential target for mood disorders as well as pain. In all studies mice

lacking functional N type channels exhibit marked decreases in the chronic and inflammatory pain responses. In contrast, mice lacking N type channels generally showed normal acute nociceptive responses.

[0010] Two examples of either FDA approved or investigational drug that act on N type channel are gabapentin and ziconotide. Gabapentin, 1 (aminomethyl) cyclohexaneacetic acid (Neurontin®), is an anticonvulsant originally found to be active in a number of animal seizure models (Taylor, et al. (1998)). Subsequent work has demonstrated that gabapentin is also successful at preventing hyperalgesia in a number of different animal pain models, including chronic constriction injury (CCI), heat hyperalgesia, inflammation, diabetic neuropathy, static and dynamic mechanoallodynia associated with postoperative pain (Taylor, et al. (1998); Cesena & Calcutt (1999); Field, et al. (1999); Cheng, J K., et al. (2000); Nicholson (2000)).

[0011] While its mechanism of action is incompletely understood, current evidence suggests that gabapentin does not directly interact with GABA receptors in many neuronal systems, but rather modulates the activity of high threshold calcium channels. Gabapentin has been shown to bind to the calcium channel $\alpha_2\delta$ ancillary subunit, although it remains to be determined whether this interaction accounts for its therapeutic effects in neuropathic pain.

[0012] In humans, gabapentin exhibits clinically effective anti hyperalgesic activity against a wide ranging of neuropathic pain conditions. Numerous open label case studies and three large double blind trials suggest gabapentin might be useful in the treatment of pain. Doses ranging from 300 2400 mg/day were studied in treating diabetic neuropathy (Backonja, et al. (1998)), postherpetic neuralgia (Rowbotham, et al. (1998)), trigeminal neuralgia, migraine and pain associated with cancer and multiple sclerosis (Di Trapini, et al. (2000); Caraceni, et al. (1999); Houtchens, et al. (1997); see also Magnus (1999); Laird & Gidal (2000); Nicholson (2000)).

[0013] Ziconotide (Prialt®; SNX 111) is a synthetic analgesic derived from the cone snail peptide Conus magus MVIIA that has been shown to reversibly block N type calcium channels. In a variety of animal models, the selective block of N type channels via intrathecal administration of Ziconotide significantly depresses the formalin phase 2 response, thermal hyperalgesia, mechanical allodynia and post surgical pain (Malmberg and Yaksh (1994); Bowersox, et al. (1996); Sluka (1998); Wang, et al. (1998)).

[0014] Ziconotide has been evaluated in a number of clinical trials via intrathecal administration for the treatment of a variety of conditions including post herpetic neuralgia, phantom limb syndrome, HIV related neuropathic pain and intractable cancer pain (reviewed in Mathur (2000)). In phase II and III clinical trials with patients unresponsive to intrathecal

opiates, Ziconotide has significantly reduced pain scores and in a number of specific instances resulted in relief after many years of continuous pain. Ziconotide is also being examined for the management of severe post operative pain as well as for brain damage following stroke and severe head trauma (Heading (1999)). In two case studies Ziconotide has been further examined for usefulness in the management of intractable spasticity following spinal cord injury in patients unresponsive to baclofen and morphine (Ridgeway, et al. (2000)). In one instance Ziconotide decreased the spasticity from the severe range to the mild to none range with few side effects. In another patient Ziconotide also reduced spasticity to the mild range although at the required dosage significant side effects including memory loss, confusion and sedation prevented continuation of the therapy.

[0015] T type calcium channels are involved in various medical conditions. In mice lacking the gene expressing the α_{1G} subunit, resistance to absence seizures was observed (Kim, et al. (2001)). Other studies have also implicated the α_{1H} subunit in the development of epilepsy (Su, et al. (2002)). There is strong evidence that some existing anticonvulsant drugs, such as ethosuximide, function through the blockade of T type channels (Gomora, et al. (2001)).

[0016] Low voltage activated calcium channels are highly expressed in tissues of the cardiovascular system. Mibefradil, a calcium channel blocker 10 30 fold selective for T type over L type channels, was approved for use in hypertension and angina. It was withdrawn from the market shortly after launch due to interactions with other drugs (Heady, et al. (2001)).

[0017] Growing evidence suggests T type calcium channels may also be involved in pain. Both mibefradil and ethosuximide have shown anti hyperalgesic activity in the spinal nerve ligation model of neuropathic pain in rats (Dogrul, et al. (2003)).

[0018] U.S. patents 6,011,035; 6,294,533; 6,310,059; and 6,492,375; PCT publications WO 01375 and WO 01/45709; PCT publications based on PCT CA 99/00612, PCT CA 00/01586; PCT CA 00/01558; PCT CA 00/01557; PCT CA 2004/000535; and PCT CA 2004/000539, and U.S. patent applications 10/746,932 filed 23 December 2003; 10/746,933 filed 23 December 2003; 10/409,793 filed 8 April 2003; 10/409,868 filed 8 April 2003; 10/655,393 filed 3 September 2003; 10/821,584 filed 9 April 2004; and 10/821,389 filed 9 April 2004 disclose calcium channel blockers where a piperidine or piperazine ring is substituted by various aromatic moieties. These applications and publications are incorporated herein by reference.

[0019] U.S. Pat. No. 5,646,149 describes calcium channel antagonists of the formula A Y B wherein B contains a piperazine or piperidine ring directly linked to Y. An essential component of these molecules is represented by A, which must be an antioxidant; the piperazine or

piperidine itself is said to be important. The exemplified compounds contain a benzhydril substituent, based on known calcium channel blockers (see below). U.S. Pat. No. 5,703,071 discloses compounds said to be useful in treating ischemic diseases. A mandatory portion of the molecule is a tropolone residue, with substituents such as piperazine derivatives, including their benzhydril derivatives. U.S. Pat. No. 5,428,038 discloses compounds indicated to exhibit a neural protective and antiallergic effect. These compounds are coumarin derivatives which may include derivatives of piperazine and other six membered heterocycles. A permitted substituent on the heterocycle is diphenylhydroxymethyl. Thus, approaches in the art for various indications which may involve calcium channel blocking activity have employed compounds which incidentally contain piperidine or piperazine moieties substituted with benzhydril but mandate additional substituents to maintain functionality.

[0020] Certain compounds containing both benzhydril moieties and piperidine or piperazine are known to be calcium channel antagonists and neuroleptic drugs. For example, Gould, R. J., et al., Proc Natl Acad Sci USA (1983) 80:5122 5125 describes antischizophrenic neuroleptic drugs such as lidoflazine, fluspirilene, pimozide, clopimozide, and penfluridol. It has also been shown that fluspirilene binds to sites on L type calcium channels (King, V. K., et al., J Biol Chem (1989) 264:5633 5641) as well as blocking N type calcium current (Grantham, C. J., et al., Brit J Pharmacol (1944) 111:483 488). In addition, Lomerizine, as developed by Kanebo, K. K., is a known calcium channel blocker. However, Lomerizine is not specific for N type channels. A review of publications concerning Lomerizine is found in Dooley, D., Current Opinion in CPNS Investigational Drugs (1999) 1:116 125.

[0021] U.S. patent publication 2002/0019389 published 14 February 2002 discloses what are characterized as urea derivatives useful as anticancer agents. Among these derivatives are piperazines wherein one ring nitrogen forms a urea with a benzhydril group. Certain of these compounds contain 3,5 dimethylphenyl or benzhydril coupled to the alternate piperazine nitrogen. These compounds are described simply as anticancer agents and are not reported to have any effects on calcium ion channels or any indications mediated by such channels.

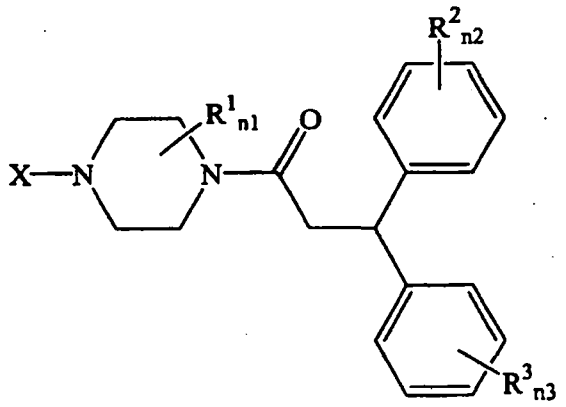
[0022] The foregoing publications are listed for convenience, and are not to be construed as prior art.

[0023] The present invention provides additional compounds which comprise benzhydril coupled to an acetyl group in turn coupled to a piperazine ring. The piperazine ring is, in turn, substituted by a variety of substituents, none of them antioxidants. These compounds are effective in blocking calcium ion channels.

Disclosure of the Invention

[0024] The invention relates to compounds useful in treating conditions such as stroke, anxiety, overactive bladder, inflammatory bowel disease, irritable bowel syndrome, interstitial colitis, head trauma, migraine, chronic, neuropathic and acute pain, drug and alcohol addiction, neurodegenerative disorders, psychoses, sleep disorders, depression, epilepsy, diabetes, cancer, male contraception, hypertension, pulmonary hypertension, cardiac arrhythmias, congestive heart failure, angina pectoris and other indications associated with calcium metabolism, including synaptic calcium channel-mediated functions.

[0025] Thus, in one aspect, the invention is directed to compounds of the formula



(1)

including the salts and conjugates thereof,

wherein each R^1-R^3 is independently a non-interfering substituent;

wherein a combination of R^2 and R^3 may form a bridge between phenyl groups which may be a bond, a CR_2 group, an NR group, O, or S wherein the S is optionally oxidized;

n^1 is 0-4 and n^2 and n^3 are independently 0-5; and

wherein X is selected from the group consisting of:

(a) optionally substituted alkyl (1-12C) or optionally substituted alkenyl (2-12C) optionally including one or more N, O or S with the proviso that any N included in a ring is secondary or is tertiary solely because of an alkyl substitution;

(b) optionally substituted aryl, provided that if n^1 is 0, and aryl is phenyl or pyridyl, said aryl must contain at least one substituent and wherein if said aryl is phenyl and contains only one substituent, said substituent must comprise an aryl group or a trialkylsilyl group and wherein said phenyl is not 2,3-dimethylphenyl or fused to an aliphatic ring;

(c) CO-aryl or CRH-aryl wherein R is H, alkyl, or a heteroaromatic ring, wherein when R is H, aryl is optionally substituted 4-pyridyl, or is substituted phenyl (other than phenyl fused to an aliphatic ring) or is substituted naphthyl or is substituted 5-membered aryl; and

(d) alkylene-aryl or alkylene-cyclocarbyl wherein said alkylene contains at least 2 C, and further optionally contains one heteroatom and/or is substituted by =O and/or OH provided that if said alkylene is CH_2CH_2, $CH_2CH_2CH_2$, CH_2CH_2O or $CH_2CH_2CH_2O$, and said aryl is phenyl, said phenyl must be substituted; and if said alkylene is $CH_2CH_2CH_2O$ substituted by OH, said aryl is other than substituted quinolyl or monosubstituted phenyl.

[0026] Non-interfering substituents are, generally, optionally substituted alkyl (1-12C), alkenyl (2-12C), alkynyl (2-12C), aryl (6-12C) or arylalkyl, arylalkenyl or arylalkynyl (each 7-16C) wherein in each of the foregoing 1-4C may be replaced by a heteroatom (Si,N, O and/or S) and wherein said optional substituents may include =O. When alkyl, alkenyl, or alkynyl comprises at least one cyclic moiety, the number of C contained may be as many as 15, again wherein one or more C may be replaced by a heteroatom. Thus, for example, R^1-R^3 may independently be in the form of an acyl, amide, or ester linkage with the ring carbon to which it is bound.

[0027] "Non-interfering substituents" also include halo, CF_3, OCF_3, CN, NO_2, NR_2, OR, SR, COOR, or $CONR_2$, wherein R is H or optionally substituted alkyl, alkenyl, alkynyl, aryl, or arylalkyl as described above. Two substituents at adjacent positions on the same ring may form a 3-7 membered saturated or unsaturated ring fused to said substituted ring, said fused ring optionally itself substituted and optionally contains one or more heteroatoms (N, S, O). R^1 may be keto if n^1 is 1 or 2.

[0028] The invention is also directed to methods to modulate calcium channel activity, preferably N type and T-type channel activity, using the compounds of formula (1). These compounds can be used to treat certain undesirable physiological conditions and used for the preparation of medicaments for the treatment of conditions requiring modulation of calcium channel activity, including stroke, anxiety, overactive bladder, inflammatory bowel disease, irritable bowel syndrome, interstitial colitis, head trauma, migraine, chronic, neuropathic and acute pain, drug and alcohol addiction, neurodegenerative disorders, psychoses, depression, epilepsy, diabetes, cancer, male contraception, hypertension, pulmonary hypertension, cardiac arrhythmias, congestive heart failure and angina pectoris.

[0029] In another aspect, the invention is directed to pharmaceutical compositions containing the compounds of formula (1).

Brief Description of the Drawings

[0030] Figure 1 is a graph showing the selectivity of compound P24 of the invention for N-type, P/Q-type and L-type channels.

[0031] Figure 2 is a graph showing the selectivity of compound P28 of the invention for N-type, P/Q-type and L-type channels.

Modes of Carrying out the Invention

[0032] The compounds of formula (1) useful in the methods of the invention exert their desirable effects through their ability to modulate the activity of N-type and/or T-type calcium channels. This makes them useful for treatment of certain conditions. Among such conditions where antagonist activity is desired are stroke, epilepsy, head trauma, migraine, inflammatory bowel disease and chronic, neuropathic and acute pain. Calcium flux is also implicated in other neurological disorders such as schizophrenia, anxiety, depression, other psychoses, and neural degenerative disorders. Other treatable conditions include cardiovascular conditions such as hypertension and cardiac arrhythmias. In addition, T-type calcium channels have been implicated in certain types of cancer, diabetes, infertility and sexual dysfunction.

[0033] While the compounds of formula (1) generally have this activity, availability of this class of calcium channel modulators permits a nuanced selection of compounds for particular disorders. The availability of this class of compounds provides not only a genus of general utility in indications that are affected by excessive calcium channel activity, but also provides a large number of compounds which can be mined and manipulated for specific interaction with particular forms of calcium channels. The availability of recombinantly produced calcium channels of the α_{1A}-α_{1I} and α_{1S} types set forth above, facilitates this selection process. Dubel, S.J., *et al., Proc Natl Acad Sci USA* (1992) 89:5058-5062; Fujita, Y., *et al., Neuron* (1993) 10:585-598; Mikami, A., *et al., Nature* (1989) 340:230-233; Mori, Y., *et al., Nature* (1991) 350:398-402; Snutch, T.P., *et al., Neuron* (1991) 7:45-57; Soong, T.W., *et al., Science* (1993) 260:1133-1136; Tomlinson, W.J., *et al., Neuropharmacology* (1993) 32:1117-1126; Williams, M.E., *et al., Neuron* (1992) 8:71-84; Williams, M.E., *et al., Science* (1992) 257:389-395; Perez-Reyes, *et al., Nature* (1998) 391:896-900; Cribbs, L.L., *et al., Circulation Research* (1998) 83:103-109; Lee, J.H., *et al., Journal of Neuroscience* (1999) 19:1912-1921.

[0034] It is known that calcium channel activity is involved in a multiplicity of disorders, and particular types of channels are associated with particular conditions. The association of

N-type channels in conditions associated with neural transmission would indicate that compounds of the invention which target N-type channels are most useful in these conditions. Many of the members of the genus of compounds of formula (1) exhibit high affinity for N-type channels and/or T-type channels. Thus, as described below, they are screened for their ability to interact with N-type and T-type channels as an initial indication of desirable function. It is desirable that the compounds exhibit IC_{50} values of <1 μM. The IC_{50} is the concentration which inhibits 50% of the calcium flux at a particular applied potential.

[0035] Illustrative conditions mediated by N-type channels are:

- Chronic pain
  - Neuropathic pain
    - Diabetic peripheral neuropathy
    - Post-herpetic neuralgia
    - Trigeminal neuralgia
    - AIDS related neuropathy
  - Cancer pain
  - Inflammatory pain
    - Osteoarthritis pain
    - Rheumatoid arthritis pain
    - Fibromyalgia
- Acute pain
  - Nociceptive pain
  - Post-operative pain
- Mood disorders
  - Anxiety disorders
    - Generalized anxiety disorder
    - Social anxiety disorder
    - Panic disorder
    - Obsessive compulsive disorder
    - Post-traumatic stress syndrome
  - Depression
  - Addiction
    - Cocaine dependence and withdrawal
    - Opioid dependence and withdrawal
    - Alcohol dependence and withdrawal
    - Nicotine dependence and withdrawal
- Gastrointestinal disorders
  - Inflammatory bowel disease
  - Irritable bowel syndrome

Genitourinary disorders
- Urinary incontinence
- Interstitial colitis
- Sexual dysfunction

[0036] Illustrative of conditions mediated by T-type channels are:

Cardiovascular disease
- Hypertension
- Arrhythmia
  - Atrial fibrillation
- Congestive heart failure
- Angina pectoris

Epilepsy
- Partial seizures
  - Temporal lobe epilepsy
- Absence seizures
- Generalized seizures
- Tonic/clonic seizures

Diabetes

Cancer

Chronic pain
- Neuropathic pain
  - Diabetic peripheral neuropathy
  - Post-herpetic neuralgia
  - Trigeminal neuralgia
  - Cancer pain
  - AIDS related neuropathy
- Inflammatory pain
  - Osteoarthritis pain
  - Rheumatoid arthritis pain
  - Fibromyalgia

Acute pain
- Nociceptive pain
- Post-operative pain

[0037] There are three distinguishable types of calcium channel inhibition. The first, designated "open channel blockage," is conveniently demonstrated when displayed calcium channels are maintained at an artificially negative resting potential of about -100 mV (as distinguished from the typical endogenous resting maintained potential of about -70 mV). When the displayed channels are abruptly depolarized under these conditions, calcium ions are caused to flow through the channel and exhibit a peak current flow which then decays. Open channel

blocking inhibitors diminish the current exhibited at the peak flow and can also accelerate the rate of current decay.

[0038] This type of inhibition is distinguished from a second type of block, referred to herein as "inactivation inhibition." When maintained at less negative resting potentials, such as the physiologically important potential of -70 mV, a certain percentage of the channels may undergo conformational change, rendering them incapable of being activated -- *i.e.*, opened -- by the abrupt depolarization. Thus, the peak current due to calcium ion flow will be diminished not because the open channel is blocked, but because some of the channels are unavailable for opening (inactivated). "Inactivation" type inhibitors increase the percentage of receptors that are in an inactivated state.

[0039] A third type of inhibition is designated "resting channel block". Resting channel block is the inhibition of the channel that occurs in the absence of membrane depolarization, that would normally lead to opening or inactivation. For example, resting channel blockers would diminish the peak current amplitude during the very first depolarization after drug application without additional inhibition during the depolarization.

[0040] In order to be maximally useful in treatment, it is also helpful to assess the side reactions which might occur. Thus, in addition to being able to modulate a particular calcium channel, it is desirable that the compound has very low activity with respect to the HERG K^+ channel which is expressed in the heart. Compounds that block this channel with high potency may cause reactions which are fatal. Thus, for a compound that modulates the calcium channel, it should also be shown that the HERG K^+ channel is not inhibited. Similarly, it would be undesirable for the compound to inhibit cytochrome p450 since this enzyme is required for drug detoxification. Finally, the compound will be evaluated for calcium ion channel type specificity by comparing its activity among the various types of calcium channels, and specificity for one particular channel type is preferred. The compounds which progress through these tests successfully are then examined in animal models as actual drug candidates.

The Invention Compounds

[0041] The substituents on the basic structures of formula (1) are described above. These include alkyl, alkenyl, alkynyl, etc., substituents.

[0042] As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight-chain, branched-chain and cyclic monovalent substituents, containing only C and H when they are

unsubstituted or unless otherwise noted. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butynyl, and the like. Typically, the alkyl, alkenyl and alkynyl substituents contain 1-10C (alkyl) or 2-12C (alkenyl or alkynyl). They may contain 1-6C (lower alkyl) or 2-6C (lower alkenyl or lower alkynyl), however, when the alkyl, alkenyl or alkynyl groups contain rings, they may contain as many as 18C, some of which may optionally be replaced by heteroatoms.

[0043] Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined but may contain one or more O, S or N heteroatoms or combinations thereof within the backbone residue. In general, the terms alkyl, alkenyl and alkynyl include those wherein heteroatoms are contained when thus specified.

[0044] As used herein, "acyl" encompasses the definitions of alkyl, alkenyl, alkynyl, each of which is coupled to an additional residue through a carbonyl group. Heteroacyl includes the related heteroforms.

[0045] "Aromatic" moiety or "aryl" moiety refers to a monocyclic or fused bicyclic moiety such as phenyl or naphthyl which may also be heteroaromatic; "heteroaromatic" also refers to monocyclic or fused bicyclic ring systems containing one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits inclusion of 5-membered rings as well as 6-membered rings. Thus, typical aromatic/heteroaromatic systems include pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl and the like. Because tautomers are theoretically possible, phthalimido is also considered aromatic. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition. Typically, the ring systems contain 5-12 ring member atoms.

[0046] Similarly, "arylalkyl" and "heteroarylalkyl" refer to aromatic and heteroaromatic systems which are coupled to another residue through a carbon chain, including substituted or unsubstituted, saturated or unsaturated, carbon chains, typically of 1-8C, or the hetero forms thereof. These carbon chains may also include a carbonyl group, thus making them able to provide substituents as an acyl or heteroacyl moiety.

[0047] "Carbocylcyl" refers to a 4-7 membered ring, said ring members being only C atoms, which ring may be saturated or unsaturated.

[0048] In general, any alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, acyl, carbocyclyl or aryl group or heteroforms as defined in formula (1) or contained in a substituent

may itself optionally be substituted by additional substituents. The nature of these substituents is similar to those recited with regard to the primary substituents themselves. Thus, where an embodiment of a substituent is alkyl, this alkyl may optionally be substituted by the remaining substituents listed as substituents where this makes chemical sense, and where this does not undermine the size limit of alkyl *per se*; *e.g.*, alkyl substituted by alkyl or by alkenyl would simply extend the upper limit of carbon atoms for these embodiments. However, alkyl substituted by aryl, amino, alkoxy, and the like would be included.

[0049] Non-interfering substituents on aryl groups in general include, but are not limited to, optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, and acyl, as well as halo, -CN, $-CF_3$, -NO, $-NO_2$, -OR, $-NR_2$, -SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, $-OCONR_2$, -RCO, -COOR, -NRSOR, $-NRSO_2R$, $-SO_3R$, $-CONR_2$, $-SO_2NR_2$, wherein each R is independently H or alkyl (1-8C), and the like.

[0050] The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, *i.e.*, acids such as hydrochloric, sulphuric, citric, acetic, or tartaric acids and bases such as potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like. Methods for preparation of the appropriate salts are well-established in the art.

[0051] In addition, in some cases, the compounds of the invention contain one or more chiral centers. The invention includes the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity.

[0052] The compounds of the invention may also be conjugated to additional entities such as polyethylene glycol (PEG), a targeting agent such as an antibody or ligand, a solid matrix such as derivatized cellulose, and the like.

Synthesis of the Invention Compounds

[0053] The compounds of the invention modulate the activity of calcium channels; in general, said modulation is the inhibition of the ability of the channel to transport calcium. As described below, the effect of a particular compound on calcium channel activity can readily be ascertained in a routine assay whereby the conditions are arranged so that the channel is

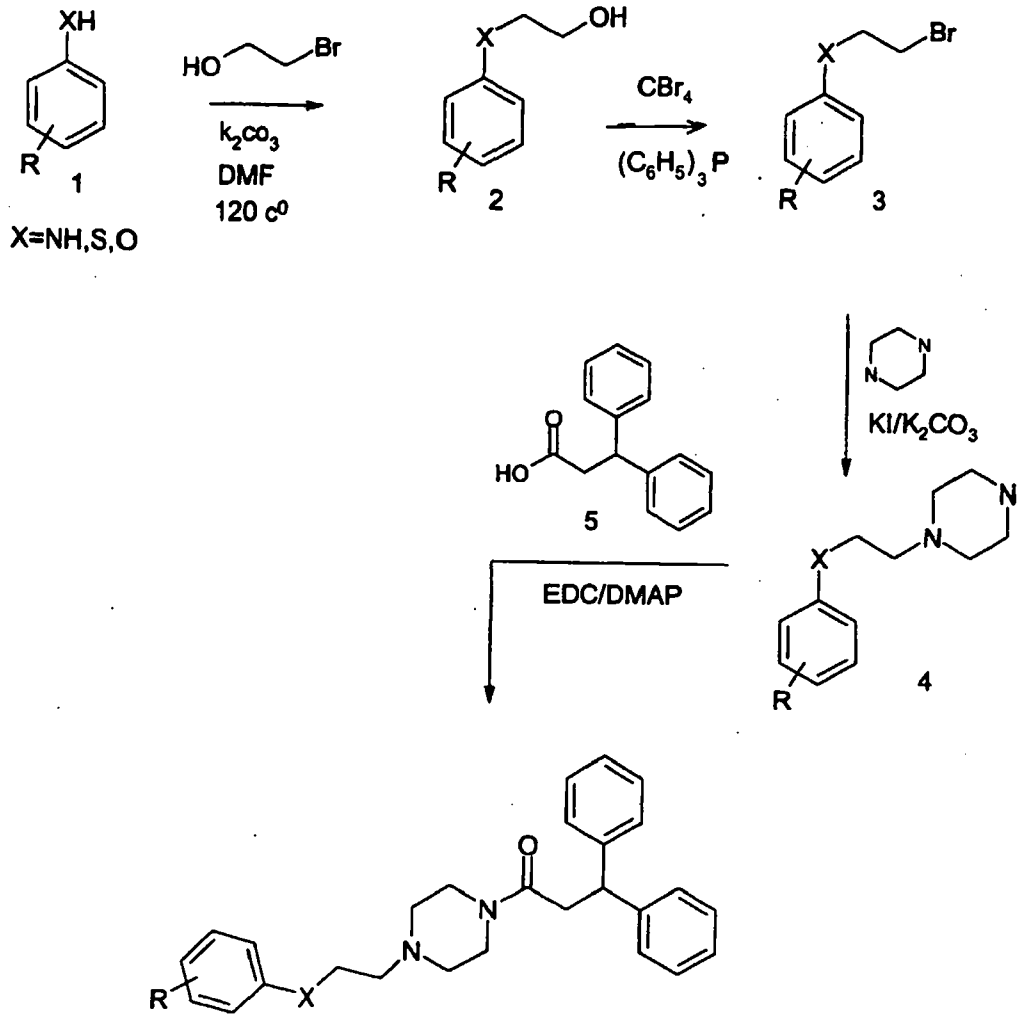
activated, and the effect of the compound on this activation (either positive or negative) is assessed. Typical assays are described hereinbelow.

[0054] The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, citric, acidic, or tartaric acids and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like. Methods for preparation of the appropriate salts are well-established in the art, as are methods of conjugation.

[0055] The compounds of the invention may be synthesized using conventional methods. Illustrative of such methods are Schemes 1 to 3.:

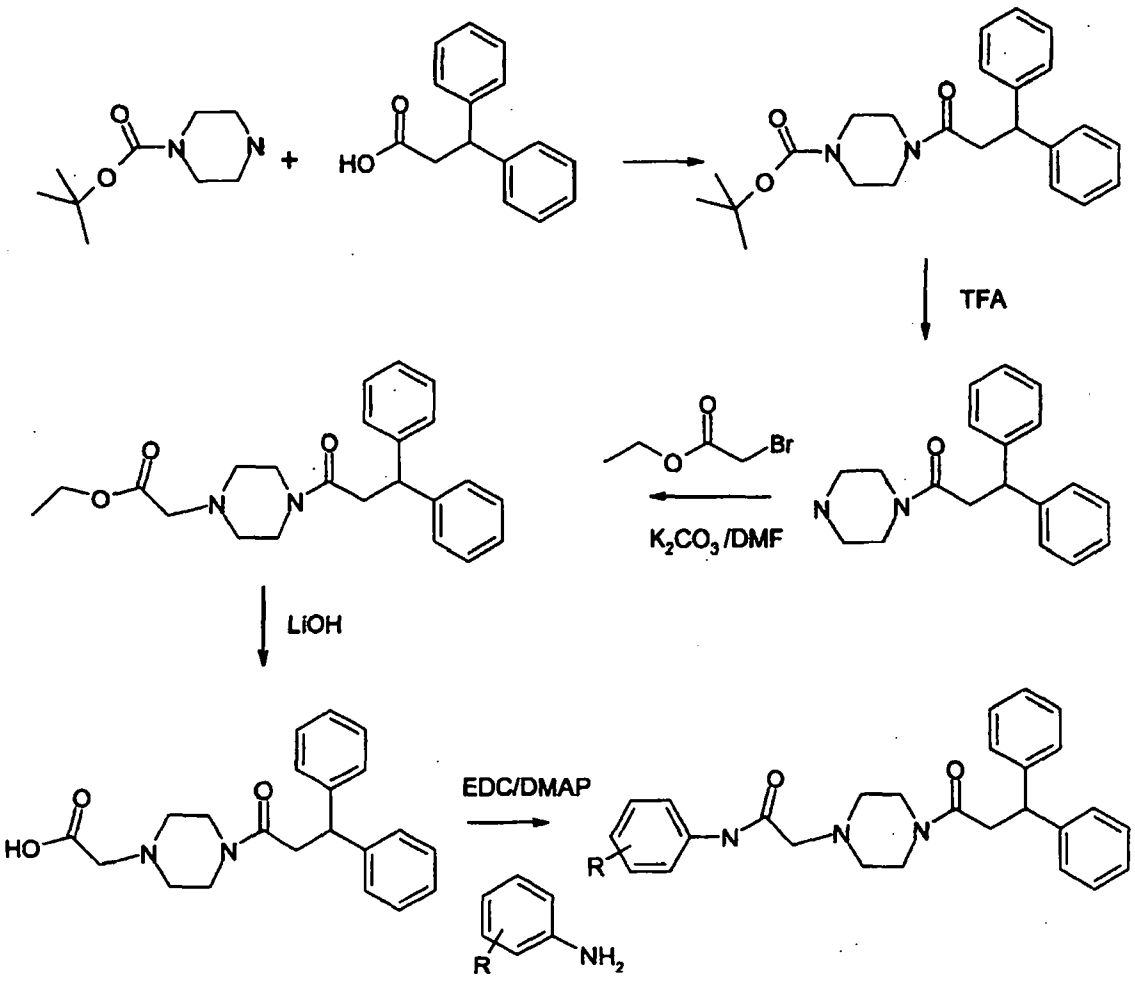
[0056] Reaction Scheme 1 was used to prepare compounds P6-P8, P25, P30-P32, P36-P42 of the invention.

Reaction Scheme 1



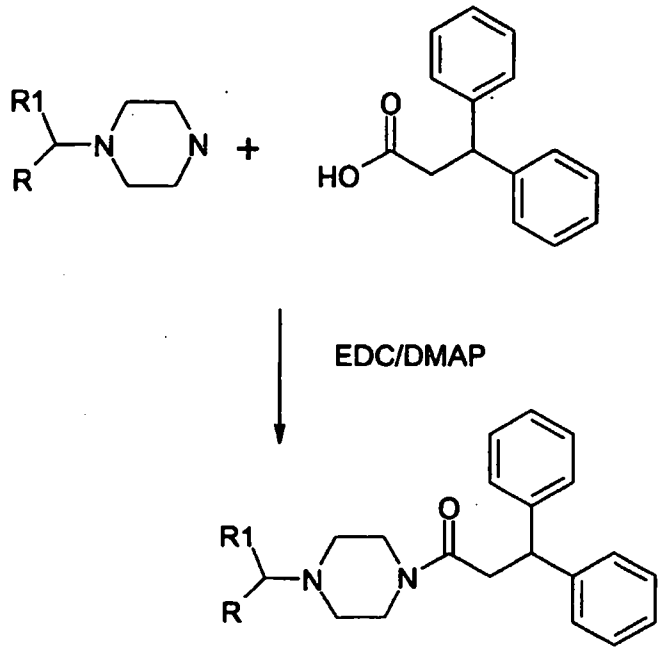
[0057] Reaction Scheme 2 was used to prepare compounds P9 and P10 of the invention.

Reaction Scheme 2



[0058] Reaction Scheme 3 was used to prepare compounds P1-P5, P12-P24, P27-P29, P33-P35 of the invention.

Reaction Scheme 3



Preferred Embodiments

[0059] The compounds of formula (1) are defined as shown in terms of the embodiments of their various substituents.

[0060] Particularly preferred embodiments of Formula (1) are those wherein only zero, one or two of the depicted rings are substituted and wherein the number of substituents on a single ring is three or less. Particularly preferred substituents for the phenyl rings shown include halo, especially fluoro or chloro,; CF_3; optionally substituted, optionally heteroatom-containing alkyl, alkenyl, aryl, alkyl aryl, alkenyl aryl, phenoxy, and the like. Where the substituents on these moieties contain alkyl or aryl groups, these also may optionally be substituted. Also preferred are bridging substituents containing heteroatoms.

[0061] Particularly preferred substituents for the piperazine ring include =O, COOR, especially COOH and COOEt, alkyl, and alkenyl, (as defined above and optionally containing heteroatoms and all optionally substituted) and halo.

[0062] Preferred embodiments of X include unsubstituted alkyl or alkenyl, including embodiments wherein one or two carbons are replaced by N, S or O. Also preferred are embodiments wherein X is arylalkyl, especially wherein the aryl moiety is phenyl and wherein the alkyl moiety contains at least one heteroatom and/or is substituted by at least one = O. Also preferred are embodiments wherein X is alkyl and is in a cyclic form, and thus may contain up to 15C, wherein one or more of said C may optionally be replaced by a heteroatom. Also preferred are embodiments wherein X comprises a heteroaryl moiety, such as pyridyl, pyrimidyl, benzimidazole, benzothiazole and the like. Also preferred are embodiments wherein X is arylalkyl wherein the alkyl group is substituted by an aromatic or other cyclic moiety; especially preferred are those embodiments wherein the alkyl portion is methylene substituted by a cyclic moiety. Also preferred are embodiments wherein X is arylalkyl, the aryl portion is phenyl and is multiply substituted or is substituted by a substituent that comprises an additional aryl moiety.

Libraries and Screening

[0063] The compounds of the invention can be synthesized individually using methods known in the art *per se*, or as members of a combinatorial library.

[0064] Synthesis of combinatorial libraries is now commonplace in the art. Suitable descriptions of such syntheses are found, for example, in Wentworth, Jr., P., *et al., Current Opinion in Biol.* (1993) 9:109-115; Salemme, F.R., *et al., Structure* (1997) 5:319-324. The libraries contain compounds with various substituents and various degrees of unsaturation, as well as different chain lengths. The libraries, which contain, as few as 10, but typically several hundred members to several thousand members, may then be screened for compounds which are particularly effective against a specific subtype of calcium channel, *i.e.*, the N-type channel. In addition, using standard screening protocols, the libraries may be screened for compounds which block additional channels or receptors such as sodium channels, potassium channels and the like.

[0065] Methods of performing these screening functions are well known in the art. These methods can also be used for individually ascertaining the ability of a compound to agonize or antagonize the channel. Typically, the channel to be targeted is expressed at the surface of a recombinant host cell such as human embryonic kidney cells. The ability of the members of the library to bind the channel to be tested is measured, for example, by the ability of the compound in the library to displace a labeled binding ligand such as the ligand normally associated with the channel or an antibody to the channel. More typically, ability to antagonize the channel is

measured in the presence of calcium ion and the ability of the compound to interfere with the signal generated is measured using standard techniques. In more detail, one method involves the binding of radiolabeled agents that interact with the calcium channel and subsequent analysis of equilibrium binding measurements including, but not limited to, on rates, off rates, K_d values and competitive binding by other molecules.

[0066] Another method involves the screening for the effects of compounds by electrophysiological assay whereby individual cells are impaled with a microelectrode and currents through the calcium channel are recorded before and after application of the compound of interest.

[0067] Another method, high-throughput spectrophotometric assay, utilizes loading of the cell lines with a fluorescent dye sensitive to intracellular calcium concentration and subsequent examination of the effects of compounds on the ability of depolarization by potassium chloride or other means to alter intracellular calcium levels.

[0068] As described above, a more definitive assay can be used to distinguish inhibitors of calcium flow which operate as open channel blockers, as opposed to those that operate by promoting inactivation of the channel. The methods to distinguish these types of inhibition are more particularly described in the examples below. In general, open-channel blockers are assessed by measuring the level of peak current when depolarization is imposed on a background resting potential of about -100 mV in the presence and absence of the candidate compound. Successful open-channel blockers will reduce the peak current observed and may accelerate the decay of this current. Compounds that are inactivated channel blockers are generally determined by their ability to shift the voltage dependence of inactivation towards more negative potentials. This is also reflected in their ability to reduce peak currents at more depolarized holding potentials (*e.g.*, -70 mV) and at higher frequencies of stimulation, *e.g.*, 0.2 Hz vs. 0.03 Hz.

Utility and Administration

[0069] For use as treatment of human and animal subjects, the compounds of the invention can be formulated as pharmaceutical or veterinary compositions. Depending on the subject to be treated, the mode of administration, and the type of treatment desired -- *e.g.*, prevention, prophylaxis, therapy; the compounds are formulated in ways consonant with these parameters.

A summary of such techniques is found in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Co., Easton, PA, incorporated herein by reference.

[0070] In general, for use in treatment, the compounds of formula (1) may be used alone, as mixtures of two or more compounds of formula (1) or in combination with other pharmaceuticals. Depending on the mode of administration, the compounds will be formulated into suitable compositions to permit facile delivery.

[0071] Formulations may be prepared in a manner suitable for systemic administration or topical or local administration. Systemic formulations include those designed for injection (*e.g.*, intramuscular, intravenous or subcutaneous injection) or may be prepared for transdermal, transmucosal, or oral administration. The formulation will generally include a diluent as well as, in some cases, adjuvants, buffers, preservatives and the like. The compounds can be administered also in liposomal compositions or as microemulsions.

[0072] For injection, formulations can be prepared in conventional forms as liquid solutions or suspensions or as solid forms suitable for solution or suspension in liquid prior to injection or as emulsions. Suitable excipients include, for example, water, saline, dextrose, glycerol and the like. Such compositions may also contain amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as, for example, sodium acetate, sorbitan monolaurate, and so forth.

[0073] Various sustained release systems for drugs have also been devised. See, for example, U.S. Patent No. 5,624,677.

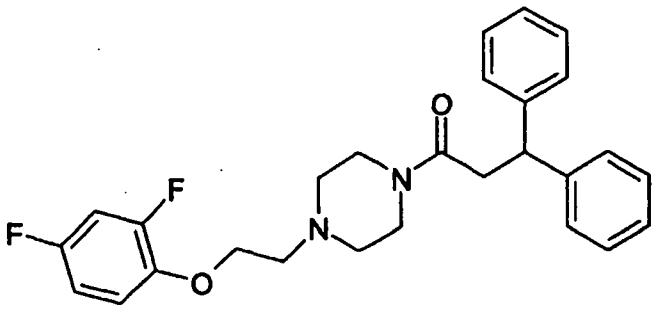
[0074] Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds of the invention. Suitable forms include syrups, capsules, tablets, as in understood in the art.

[0075] For administration to animal or human subjects, the dosage of the compounds of the invention is typically 0.1-15 mg/kg, preferably 0.1-1 mg/kg. However, dosage levels are highly dependent on the nature of the condition, the condition of the patient, the judgment of the practitioner, and the frequency and mode of administration.

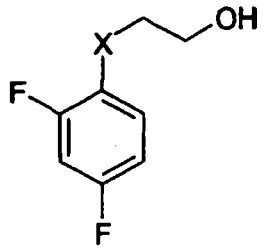
[0076] The following examples are intended to illustrate but not to limit the invention.

Example 1

Synthesis of 1-{4-[2-(2,4-difluoro-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one

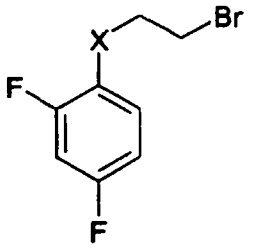


A. Synthesis of 2-(2,4-difluoro-phenoxy)-ethanol



[0077] K_2CO_3 (1.07g, 7.78 mmol) was added to a solution of 2,4-difluoro phenol(0.84g, 6.48 mmol) in dry DMF (15 ml). 2-Bromoethanol (0.81g, 6.48 mmol) was added, and the mixture was heated overnight at 120°C. The mixture was cooled, taken up in EtOAc, extracted with water (20 ml), saturated NaCl (4x 20 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The product was purified by column chromatography on silica (Hexane:EtOAc 3:1) to give the desired product in 63% yield

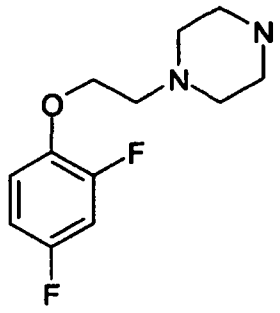
B. Synthesis of 4-(2-bromo-ethoxy)-1,3-difluoro benzene



[0078] To a cool solution 2-(2,4-difluoro-phenoxy)-ethanol (0.48g, 2.77 mmol.) in CH_2Cl_2 (15 ml), triphenyl phosphine (1.3g, 5 mmol)) was added. Carbon tetrabromide (1.65g, 5 mmol.) in CH_2Cl_2 (3 ml) was added to the solution dropwise under N_2. The solution was stirred for 30 minutes. EtOAc was added, then the solvent was evaporated under reduced pressure.

[0079] The product was purified by column chromatography on silica (Hexane:EtOAc 1:1) to give the desired product in 83% yield.

C. Synthesis of 1-[2-(2,4-difluoro-phenoxy)-ethyl]-piperazine

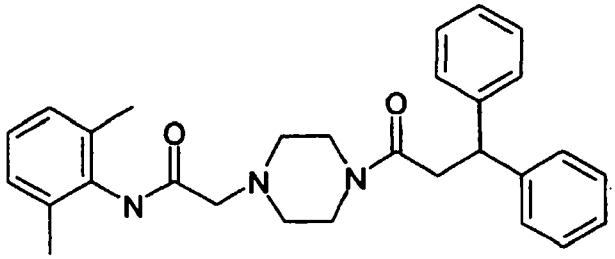


[0080] A mixture of piperazine (8.7g, 101.26 mmol) in butanone (70ml), 4-(2-bromo-ethoxy)-1,3-difluoro benzene (6.0g, 25.31 mmol), anhydrous K_2CO_3 (3.5g, 25.31 mmol) and KI (4.2g, 25.31 mmol) was refluxed under nitrogen for 18 hours. The mixture was then cooled and filtered and the solvent removed in vacuo. The residue was dissolved in CH_2Cl_2 (200 ml) and washed with water (50ml). Drying and removal of the solvent followed by chromatography (CH_2Cl_2: CH_3OH: NH_4OH 10:1) afforded desired product in 73% yield.

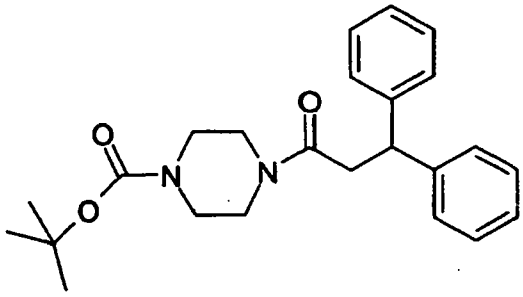
[0081] To a solution of 1-[2-(2,4-difluoro-phenoxy)-ethyl]-piperazine (1.0g, 4.13 mmol) in dry CH_2Cl_2 (30 ml) was added 3,3-diphenylpropanoic acid (1.12g, 4.95 mmol) under nitrogen. To the reaction was added EDC (1.0g, 5.36 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (150ml). The organic was washed with water (30ml, 2x) and 10% NaOH (30 ml) and dried over $MgSO_4$ and evaporated to dryness. The resulting residue was purified by column chromatography using ethyl acetate to give desired product in 85% yield.

Example 2

Synthesis of N-(2,6-dimethyl-phenyl)-2-[4-(3,3-diphenyl-propionyl)-piperazin-1-yl]-acetamide

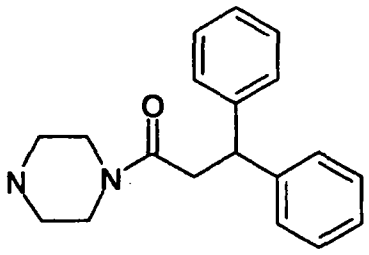


A. Synthesis of 4-(3,3-diphenyl-propionyl)-piperazine-1-carboxylic acid tert-butyl ester



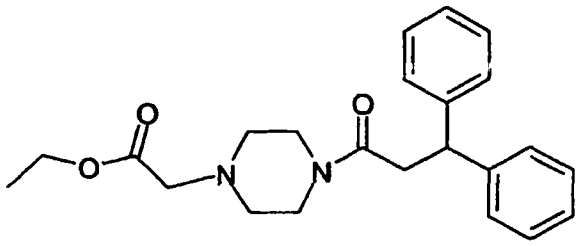
[0082] To a solution of 3,3 diphenylpropionic acid (1.45g, 6.44mmol) in dry CH_2Cl_2 (70 ml) was added mono-boc piperizine (1.32g, 7.08mmol) under nitrogen. To the reaction was added EDC (2.71g, 14.16mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (200ml). The organic was washed with water (50ml, 2x) and 10% NaOH (50 ml) and dried over $MgSO_4$ and evaporated to dryness. The resulting residue was purified by column chromatography using hexane: ethyl acetate (1:1) to give desired product in 76% yield.

B. Synthesis of 3,3-diphenyl-1-piperazin-1-yl-propan-1-one



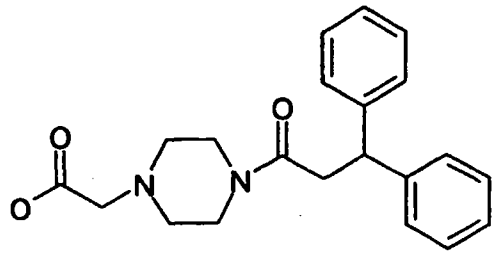
[0083] To a solution of 4-(3,3-diphenyl-propionyl)-piperazine-1-carboxylic acid tert-butyl ester (2.15g, 5.45mmol) in dry CH_2Cl_2 (60 ml) was added TFA (20 ml) and resulting mixture stirred at room temperature for 3 hrs. Solvent and excess TFA was then evaporated and the residue was dissolved in CH_2Cl_2 (150 ml) and washed with sat. $NaHCO_3$ (2X) and dried over $MgSO_4$. Evaporation of solvent gave 1.65g of pure product.

C. Synthesis of [4-(3,3-diphenyl-propionyl)-piperazin-1-yl]-acetic acid ethyl ester



[0084] To a solution of 3,3-diphenyl-1-piperazin-1-yl-propan-1-one (2.0g, 6.79mmol) and ethyl bromoacetate (0.94ml, 8.49 mmol) in dry DMF (15ml) was added K_2CO_3 (2.7g, 19.53mmol) and the mixture was heated to 70°C overnight. Reaction mixture was cooled and water (32ml) was added. The product was extracted with ether, dried and evaporated. The residue was purified by column chromatography using hexane:ethyl acetate (1:4) to give the desired product in 60% yield.

D. Synthesis of [4-(3,3-diphenyl-propionyl)-piperazin-1-yl]-acetic acid

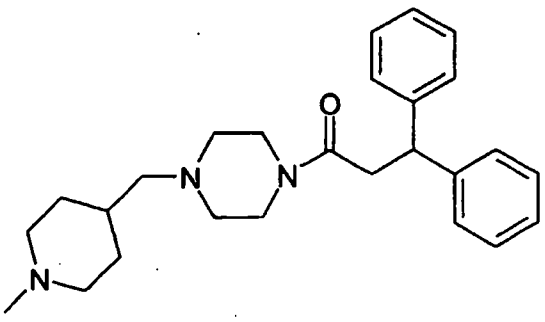


[0085] A mixture of [4-(3,3-diphenyl-propionyl)-piperazin-1-yl]-acetic acid ethyl ester (1.17g, 3.07mmol) and LiOH (645mg, 15.35mmol) in MeOH: H_2O (3:1, 40ml) stirred at room temperature for 2 days. The solvent was then evaporated and residue dissolved in water. Upon acidified with 2N HCl to pH 3, product precipitated in aq. phase, filtered and washed few times with water and dried to give the desired product in 78% yield.

[0086] To a solution of [4-(3,3-diphenyl-propionyl)-piperazin-1-yl]-acetic acid (0.8g, 2.29mmol) in dry CH_2Cl_2 (50 ml) was added 2,6-dimethyl aniline (0.28ml, 2.29mmol) under nitrogen. To the reaction was added EDC (0.87g, 4.58mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (120ml). The organic was washed with water (30ml, 2x) and 10% NaOH (30 ml) and dried over $MgSO_4$ and evaporated to dryness. The resulting residue was purified by column chromatography using CH_2Cl_2: MeOH (15:1) to give desired product in 72% yield.

Example 3

Synthesis of 1-[4-(1-methyl-piperidin-4-ylmethyl)piperazin-1-yl]-3,3-diphenyl-propan-1-one



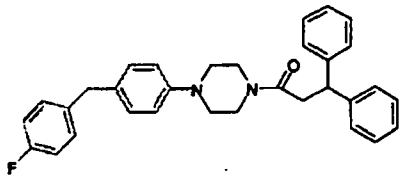
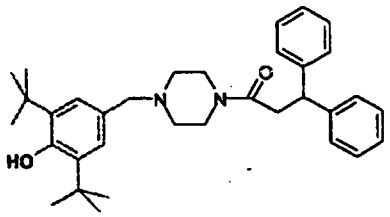
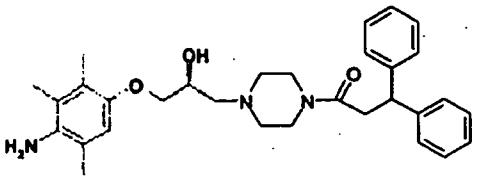
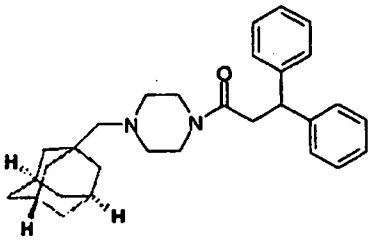
[0087] To a solution of 1-(1-methyl-piperidin-4ylmethyl)-piperazine (0.25g, 1.26 mmol) in dry CH_2Cl_2 (25 ml) was added 3,3-diphenylpropanoic acid (0.26g, 1.15 mmol) under nitrogen.

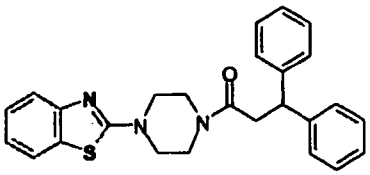
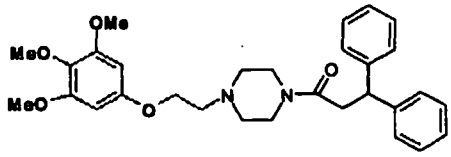
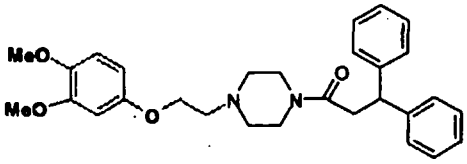
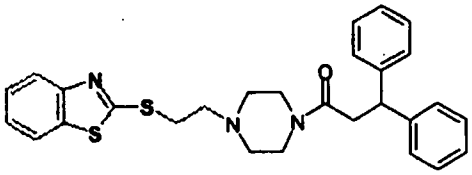
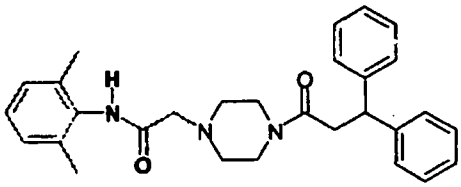
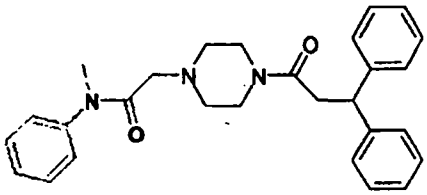
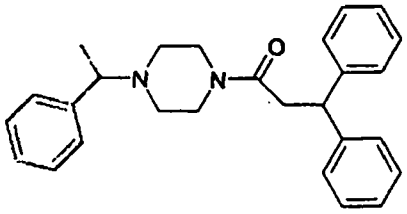
To the reaction was added EDC (0.48g, 2.53 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (100ml). The organic was washed with water (25ml, 2x) and 10% NaOH (25 ml) and dried over $MgSO_4$ and evaporated to dryness. The resulting residue was purified by column chromatography using CH_2Cl_2: MeOH (5:1) to give desired product in 69% yield.

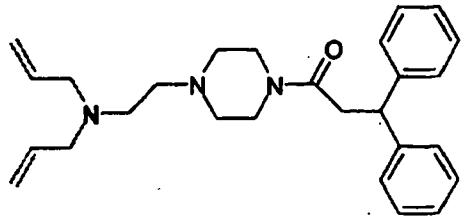
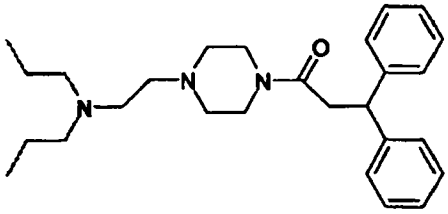
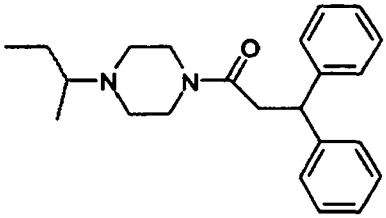
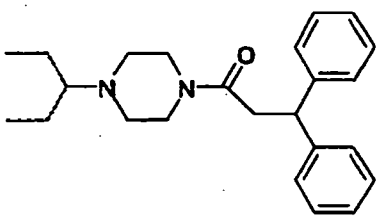
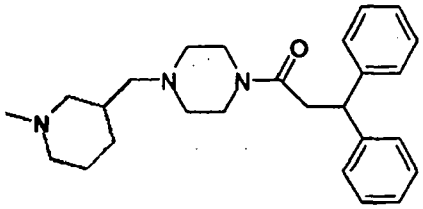
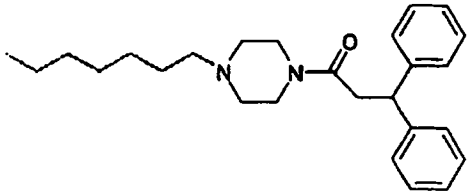
Example 4

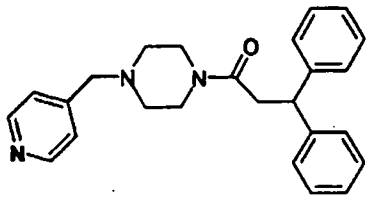
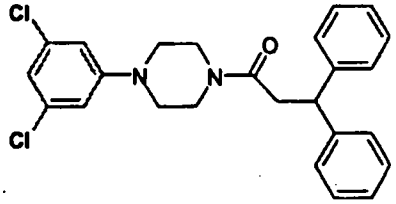
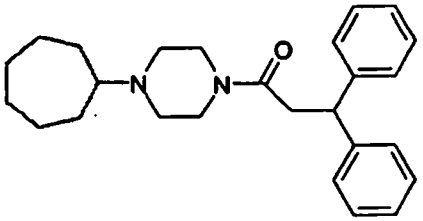
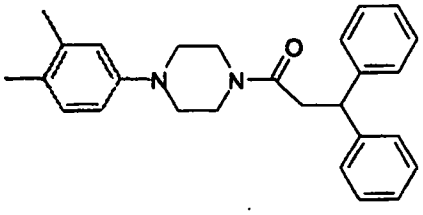
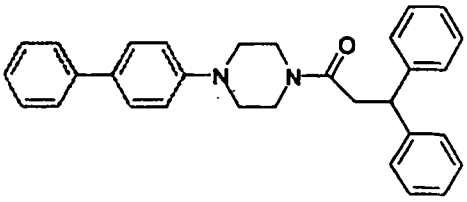
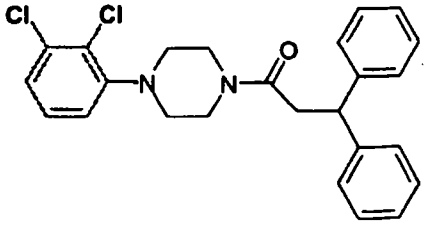
Summary of Illustrative Compounds

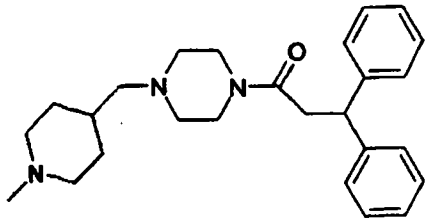
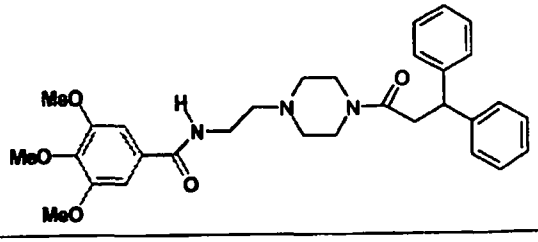
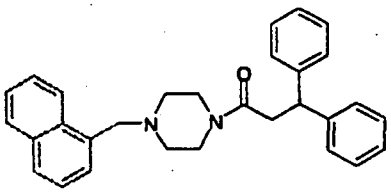
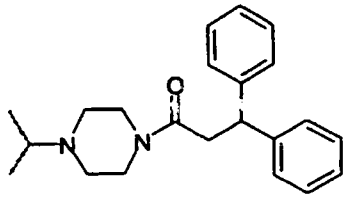
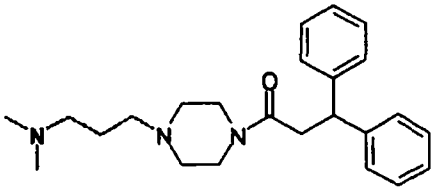
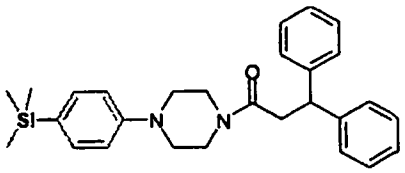
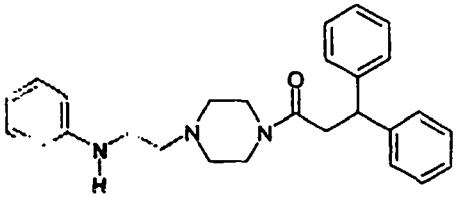
[0088] The table below shows names and structures of synthesized compounds.

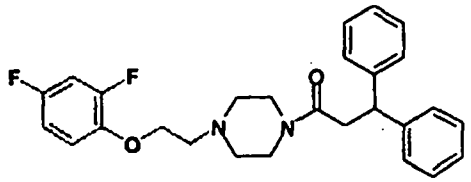
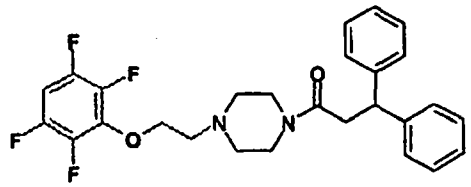
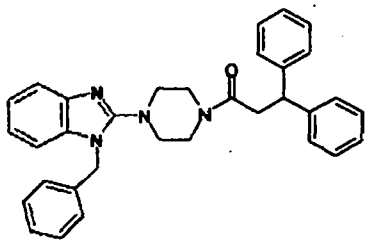
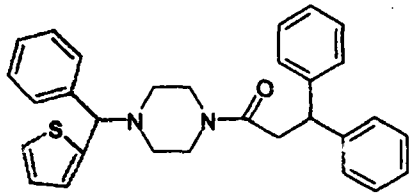
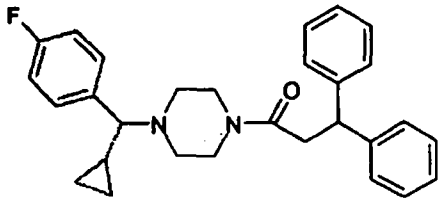
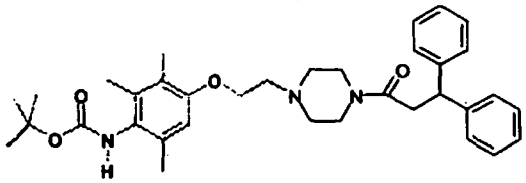
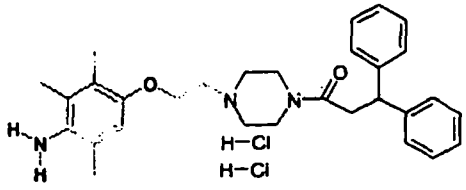
Compound Number	Name	Structure
P1	1-{4-[4-(4-Fluoro-benzyl)-phenyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P2	1-[4-(3,5-Di-tert-butyl-4-hydroxy-benzyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P3	1-{4-[3-(4-Amino-2,3,5-trimethyl-phenoxy)-2-hydroxy-propyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P4	1-(4-Adamantan-1-ylmethyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	

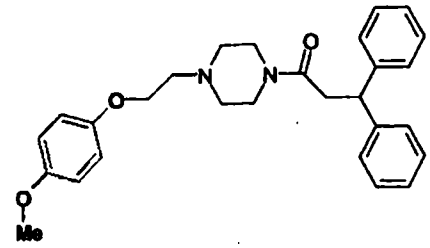
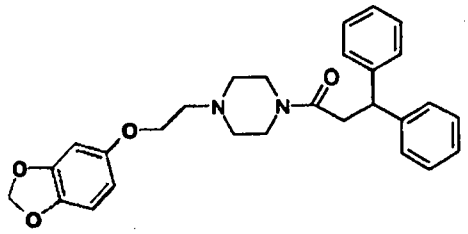
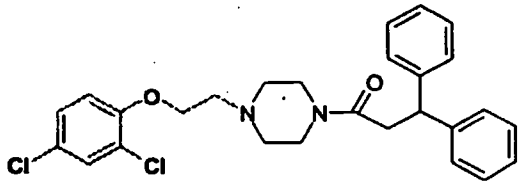
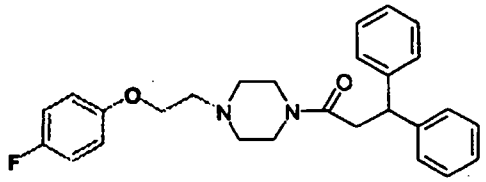
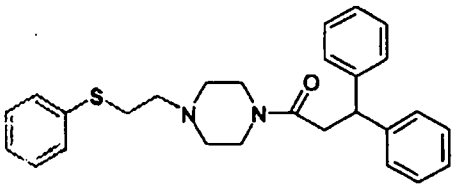
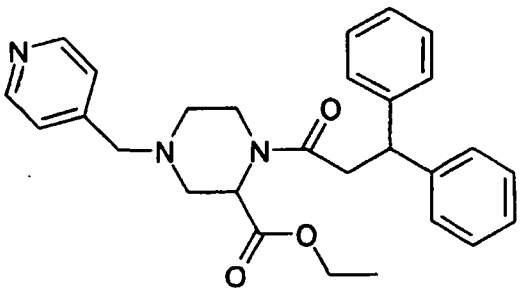
Compound Number	Name	Structure
P5	1-(4-Benzothiazol-2-yl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	
P6	3,3-Diphenyl-1-{4-[2-(3,4,5-trimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-propan-1-one	
P7	1-{4-[2-(3,4-Dimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P8	1-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P9	N-(2,6-Dimethyl-phenyl)-2-[4-(3,3-diphenyl-propionyl)-piperazin-1-yl]-acetamide	
P10	2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-N-methyl-N-phenyl-acetamide	
P11	3,3-Diphenyl-1-[4-(1-phenyl-ethyl)-piperazin-1-yl]-propan-1-one	

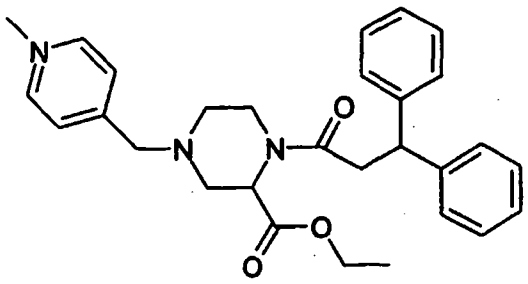
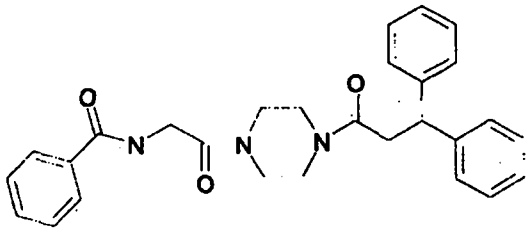
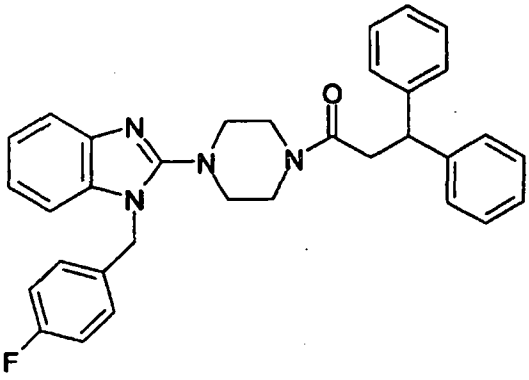
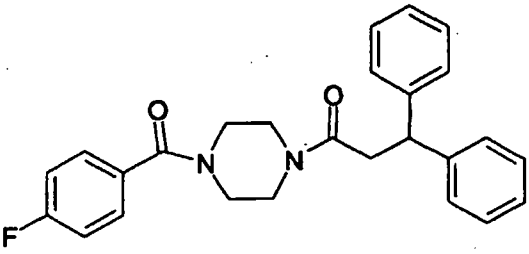
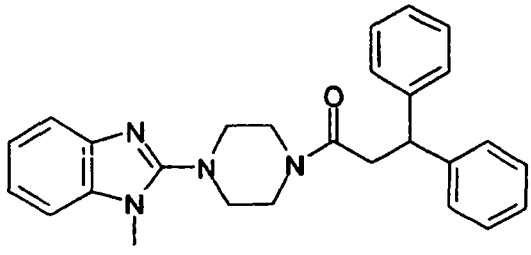
Compound Number	Name	Structure
P12	1-[4-(2-Diallylamino-ethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P13	1-[4-(2-Dipropylamino-ethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P14	1-(4-sec-Butyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	
P15	1-[4-(1-Ethyl-propyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P16	1-[4-(1-Methyl-piperidin-3-ylmethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P17	1-(4-Heptyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	

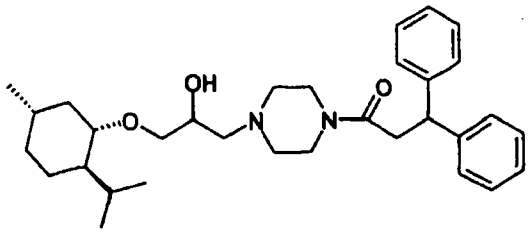
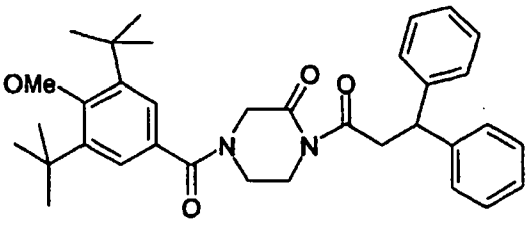
Compound Number	Name	Structure
P18	3,3-Diphenyl-1-(4-pyridin-4-ylmethyl-piperazin-1-yl)-propan-1-one	
P19	1-[4-(3,5-Dichloro-phenyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P20	1-(4-Cycloheptyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	
P21	1-[4-(3,4-Dimethyl-phenyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P22	1-(4-Biphenyl-4-yl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	
P23	1-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	

Compound Number	Name	Structure
P24	1-[4-(1-Methyl-piperidin-4-ylmethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P25	N-{2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-ethyl}-3,4,5-trimethoxy-benzamide	
P26	1-(4-Naphthalen-1-ylmethyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	
P27	1-(4-isopropyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one	
P28	1-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P29	3,3-Diphenyl-1-[4-(4-trimethylsilanyl-phenyl)-piperazin-1-yl]-propan-1-one	
P30	3,3-Diphenyl-1-[4-(2-phenylamino-ethyl)-piperazin-1-yl]-propan-1-one	

Compound Number	Name	Structure
P31	1-{4-[2-(2,4-Difluoro-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P32	3,3-Diphenyl-1-{4-[2-(2,3,5,6-tetrafluoro-phenoxy)-ethyl]-piperazin-1-yl}-propan-1-one	
P33	1-[4-(1-Benzyl-1H-benzoimidazol-2-yl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P34	3,3-Diphenyl-1-[4-(phenyl-thiophen-2-yl-methyl)-piperazin-1-yl]-propan-1-one	
P35	1-{4-[Cyclopropyl-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P36	(4-{2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-ethoxy}-2,3,6-trimethyl-phenyl)-carbamic acid tert-butyl ester	
P37	1-{4-[2-(4-Amino-2,3,5-trimethyl-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	

Compound Number	Name	Structure
P38	1-{4-[2-(4-Methoxy-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P39	1-{4-[2-(Benzo[1,3]dioxol-5-yloxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P40	1-{4-[2-(2,4-Dichloro-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P41	1-{4-[2-(4-Fluoro-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P42	3,3-Diphenyl-1-[4-(2-phenylsulfanyl-ethyl)-piperazin-1-yl]-propan-1-one	
P43	1-(3,3-Diphenyl-propionyl)-4-pyridin-4-ylmethyl-piperazine-2-carboxylic acid ethyl ester	

Compound Number	Name	Structure
P44	1-(3,3-Diphenyl-propionyl)-4-(1-methyl-pyridin-4-ylmethyl)-piperazine-2-carboxylic acid ethyl ester	
P45	N-{2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-2-oxo-ethyl}-benzamide	
P46	1-{4-[1-(4-Fluoro-benzyl)-1H-benzoimidazol-2-yl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P47	1-[4-(4-Fluoro-benzoyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P48	1-[4-(1-Methyl-1H-benzoimidazol-2-yl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	

Compound Number	Name	Structure
P49	1-{4-[2-Hydroxy-3-((1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyloxy)-propyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P50	4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-1-(3,3-diphenyl-propionyl)-piperazin-2-one	

Example 5

N-type Calcium Channel Blocking Activities of Various Invention Compounds

[0089] The methods of Example 1 were followed with slight modifications as will be apparent from the description below.

A. Transformation of HEK cells:

[0090] N-type calcium channel blocking activity was assayed in human embryonic kidney cells, HEK 293, stably transfected with the rat brain N-type calcium channel subunits ($a_{1B} + a_{2d} + \beta_{1b}$ cDNA subunits). Alternatively, N-type calcium channels ($a_{1B} + a_{2d} + \beta_{1b}$ cDNA subunits), L-type channels ($a_{1C} + a_{2d} + \beta_{1b}$ cDNA subunits) and P/Q-type channels ($a_{1A} + a_{2d} + \beta_{1b}$ cDNA subunits) were transiently expressed in HEK 293 cells. Briefly, cells were cultured in Dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum, 200 U/ml penicillin and 0.2 mg/ml streptomycin at 37°C with 5% CO_2. At 85% confluency cells were split with 0.25% trypsin/1 mM EDTA and plated at 10% confluency on glass coverslips. At 12 hours the medium was replaced and the cells transiently transfected using a standard calcium phosphate protocol and the appropriate calcium channel cDNAs. Fresh DMEM was supplied and the cells transferred to 28°C/5% CO_2. Cells were incubated for 1 to 2 days to whole cell recording.

B. Measurement of Inhibition:

[0091] Whole cell patch clamp experiments were performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, CA) linked to a personal computer equipped with pCLAMP software. The external and internal recording solutions contained, respectively, 5 mM $BaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEACl, 10 mM glucose, 87.5 mM CsCl (pH 7.2) and 108 mM CsMS, 4 mM $MgCl_2$, 9 mM EGTA, 9 mM HEPES (pH 7.2). Currents were typically elicited from a holding potential of -80 mV to +10 mV using Clampex software (Axon Instruments). Typically, currents were first elicited with low frequency stimulation (0.03 Hz) and allowed to stabilize prior to application of the compounds. The compounds were then applied during the low frequency pulse trains for two to three minutes to assess tonic block, and subsequently the pulse frequency was increased to 0.2 Hz to assess frequency dependent block. Data were analyzed using Clampfit (Axon Instruments) and SigmaPlot 4.0 (Jandel Scientific).

[0092] Using the procedure set forth in this Example 4, various compounds of the invention were tested for their ability to block N-type calcium channels. The results show IC_{50} values in the range of 0.05-1 μM, as shown in the following table.

Table 1: Block of a1B N-type Channels

Compound	0.067 Hz IC50 (μM)	0.2 Hz IC50 (μM)
P1	0.240	0.320
P2	0.387	0.292
P3	0.531	0.445
P6	0.520	0.360
P7	1.090	0.800
P9	>1	>1
P10	0.471	0.295
P11	0.660	0.480
P12	0.350	0.288
P13	0.554	0.413
P14	0.261	0.217
P15	0.534	0.321
P16	0.500	0.300
P17	0.376	0.224
P18	0.110	0.076

Compound	0.067 Hz IC50 (μM)	0.2 Hz IC50 (μM)
P19	0.280	0.180
P20	0.430	0.240
P21	0.370	0.290
P22	0.314	0.174
P23	0.650	0.410
P24	0.190	0.130
P25	0.421	0.275
P26	0.263	0.130
P27	0.715	0.371
P28	0.249	0.159
P29	0.361	0.298
P30	3.55	0.601
P31	0.597	0.398
P32	0.313	0.266
P33	0.240	0.180
P34	0.290	0.150
P35	0.520	0.430
P36	0.450	0.350
P37	0.670	0.420
P38	0.183	0.135
P39	0.400	0.280
P40	0.364	0.308
P41	0.349	0.282
P45	0.580	0.350
P46	0.350	0.270
P47	0.480	0.430
P50	0.200	0.124

Example 6

Assessment of Selective Calcium Channel Blocking Activity

[0093] Antagonist activity was measured using whole cell patch recordings on human embryonic kidney cells either stably or transiently expressing rat $\alpha_{1B}+\alpha_{2b}+\beta_{1b}$ channels (N-type channels) with 5 mM barium as a charge carrier.

[0094] For transient expression, host cells, such as human embryonic kidney cells, HEK 293 (ATCC# CRL 1573) were grown in standard DMEM medium supplemented with 2 mM glutamine and 10% fetal bovine serum. HEK 293 cells were transfected by a standard calcium-phosphate-DNA coprecipitation method using the rat $\alpha_{1B} + \beta_{1b} + \alpha_2\delta$ N-type calcium channel subunits in a vertebrate expression vector (for example, see *Current Protocols in Molecular Biology*).

[0095] After an incubation period of from 24 to 72 hrs the culture medium was removed and replaced with external recording solution (see below). Whole cell patch clamp experiments were performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, CA) linked to an IBM compatible personal computer equipped with pCLAMP software. Borosilicate glass patch pipettes (Sutter Instrument Co., Novato, CA) were polished (Microforge, Narishige, Japan) to a resistance of about 4 MΩ when filled with cesium methanesulfonate internal solution (composition in MM: 109 $CsCH_3SO_4$, 4 $MgCl_2$, 9 EGTA, 9 HEPES, pH 7.2). Cells were bathed in 5 mM Ba^{++} (in mM: 5 $BaCl_2$, 1 $MgCl_2$, 10 HEPES, 40 tetraethylammonium chloride, 10 glucose, 87.5 CsCl pH 7.2). Current data shown were elicited by a train of 100 ms test pulses at 0.066 Hz from -100 mV and/or -80 mV to various potentials (min. -20 mV, max. +30 mV). Drugs were perfused directly into the vicinity of the cells using a microperfusion system.

[0096] Normalized dose-response curves were fit (Sigmaplot 4.0, SPSS Inc., Chicago, IL) by the Hill equation to determine IC_{50} values. Steady-state inactivation curves were plotted as the normalized test pulse amplitude following 5 s inactivating prepulses at +10 mV increments. Inactivation curves were fit (Sigmaplot 4.0) with the Boltzman equation, I_{peak} (normalized)$=1/(1+\exp((V-V_h)z/25.6))$, where V and V_h are the conditioning and half inactivation potentials, respectively, and z is the slope factor.

[0097] The table below shows the results obtained with several compounds of the invention which are selective for N-type channels. In addition, Figures 1 and 2 show the specificity of compounds P24 and P28 of the invention which selectively block N-type channels.

Selectivity of Compounds for N-type Ca^{2+} Channels

Tested at 0.1 Hz, 5 mM Ba^{2+}

Compound	N-type IC_{50} (μM)	P/Q-type IC_{50} (μM)	L-type IC_{50} (μM)	P/Q:N ratio	L:N ratio
P24	0.257	2.449	~30	9.5:1	117:1
P28	0.214	6.446	20	9.5:1	93:1

Example 7

Block of a_{1G} T-type Channels

[0098] Standard patch-clamp techniques were employed to identify blockers of T-type currents. Briefly, previously described HEK cell lines stably expressing human a_{1G} subunits were used for all the recordings (passage #: 4-20, 37° C, 5% CO_2). To obtain T-type currents, plastic dishes containing semi-confluent cells were positioned on the stage of a ZEISS AXIOVERT S100 microscope after replacing the culture medium with external solution (see below). Whole-cell patches were obtained using pipettes (borosilicate glass with filament, O.D.: 1.5 mm, I.D.: 0.86 mm, 10 cm length), fabricated on a SUTTER P-97 puller with resistance values of ~5 MO (see below for internal medium).

External Solution 500 ml – pH 7.4, 265.5 mOsm

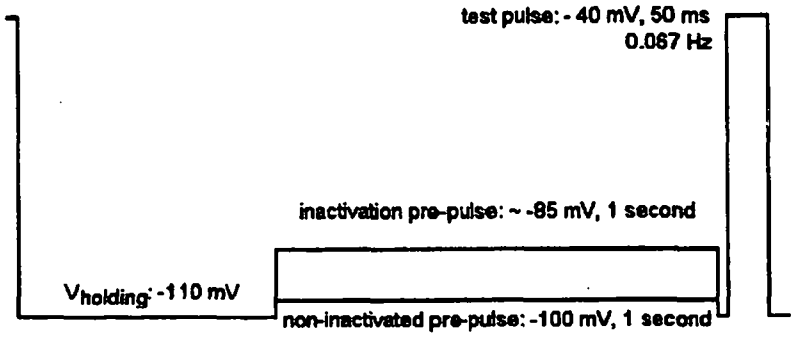
Salt	*Final mM*	*Stock M*	*Final ml*
CsCl	132	1	66
$CaCl_2$	2	1	1
$MgCl_2$	1	1	0.5
HEPES	10	0.5	10
glucose	10	----------	0.9 grams

Internal Solution 50 ml – pH 7.3 with CsOH, 270 mOsm

Salt	*Final mM*	*Stock M*	*Final ml*
Cs-Methanesulfonate	108	----------	1.231 gr/50 ml
$MgCl_2$	2	1	0.1
HEPES	10	0.5	1
EGTA-Cs	11	0.25	2.2
ATP	2	0.2	0.025 (1 aliquot / 2.5 ml)

T-type currents were reliably obtained by using two voltage protocols:
(1) "non-inactivating", and
(2) "inactivation"

[0099] In the non-inactivating protocol, the holding potential is set at –110 mV and with a pre-pulse at –100 mV for 1 second prior to the test pulse at –40 mV for 50 ms. In the inactivation protocol, the pre-pulse is at approximately –85 mV for 1 second, which inactivates about 15% of the T-type channels.



[00100] Test compounds were dissolved in external solution, 0.1-0.01 % DMSO. After ~10 min rest, they were applied by gravity close to the cell using a WPI microfil tubing. The "non-inactivated" pre-pulse was used to examine the resting block of a compound. The "inactivated" protocol was employed to study voltage-dependent block. However, the initial data shown below were mainly obtained using the non-inactivated protocol only. IC_{50} values are shown for various compounds of the invention in the following table.

Table 5: Block of a_{1G} T-type Channels

Compound	-100 mV IC50 (μM)	-80 mV IC50 (μM)
P12	10.0	1.5
P19	0.154	
P21	No effect	
P23	0.905	
P24	15.0	2.3
P28	7.8	1.8
P30	No effect	
P33	0.0088	0.0022
P41	No effect	
P45	15.0	4.2
P46	0.028	0.014
P47	no effect	10.0

References

Augustine, G.J., Charlton, M.P. & Smith, S.J. (1987) Calcium action in synaptic transmitter release. *Annu Rev Neurosci* 10: 633-693.

Backonja, M., Beydoun, A, Edwards, K.R., Schwartz, S.L. Fonesca, V., Hes, M., LaMoreaux, L. & Garofalo, E. (1998) Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *JAMA* 280: 1831-1836.

Bourinet E., Soong T.W., Sutton K., Slaymaker S., Mathews E., Monteil A., Zamponi G.W., Nargeot J. & Snutch T.P. (1999) Splicing of alpha 1A subunit gene generates phenotypic variants of P- and Q-type calcium channels. *Nature Neuroscience* 2: 407-415.

Bowersox, S.S., Gadbois, T., Singh, T., Pettus, M., Wang, Y-X & Luther, R.R. (1996) Selective N-type neuronal voltage-sensitive calcium channel blocker. SNX-111, produces spinal anticiception in rat models of acute, persistent and neuropathic pain. *J Pharmacol Exp Ther* 279: 1243-1249.

Caraceni, A., Zecca, E., Martini, C. & Conno, F. D. (1999) Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain. *J Pain & Symp Manag* 17: 441-445.

Catterall, W. (2000) Structure and regulation of voltage-gated Ca2+ channels. *Annu Rev Cell Dev Biol* 16: 521-55.

Cesena, R.M. & Calcutt, N.A. (1999) Gabapentin prevents hyperalgesia during the formalin test in diabetic rats. *Neurosci Lett* 262: 101-104.

Chaplan, S.R., Pogrel, J.W. & Yaksh, T.L. (1994) Role of voltage-dependent calcium channel subtypes in experimental tactile allodynia. *J Pharmacol Exp Ther* 269 1117-1123.

Cheng, J-K., Pan, H-L. & Eisenach, J.C. (2000) Antiallodynic effect of intrathecal gabapentin and its interaction with clonidine in a rat model of postoperative pain. *Anesthesiology* 92: 1126-1131.

Cribbs, L.L., Lee, J.H., Yang, J., Satin, J., Zhang, Y., Daud, A., Barclay, J., Williamson, M.P., Fo,x M., Rees, M. & Perez-Reyes, E. (1998) Cloning and characterization of alpha1H from human heart, a member of the T-type Ca2+ channel gene family. *Circulation Research* 83:103-109

De Waard, M., Gurnet, C.A. & Campbell, K.T. (1996) Structural and functional diversity of voltage activated calcium channels. In; Narahashi T. ed. *Ion Channels*. Plenum Press, NY.

Di Trapani, G., Mei, D., Marra, C., Mazza, S. & Capuano, A. (2000) Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study. *Clin Ter* 151: 145-148.

Dooley, D. (1999) Lomerizine. Current Opinion in CPNS Investigational Drugs 1: 116-125.

Dubel, S.J., Starr, T.V., Hell, J., Ahlijanian, M.K., Enyeart, J.J., Catterall, W.A. & Snutch, T.P. (1992) Molecular cloning of the alpha-1 subunit of an omega-conotoxin-sensitive calcium channel. *Proc Natl Acad Sci USA* 89: 5058-5062.

Dunlap, K., Luebke, J.I. & Turner, T.J. (1995) Exocytotic Ca2+ channels in mammalian central neurons. *Trends Neurosci* 18: 89-98.

Field, M.J., McCleary, S., Hughes, J. & Singh, L. (1999) Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat. *Pain* 80: 391-398.

Fujita, Y., Mynlieff, M., Dirksen, R.T., Kim, M.S., Niidome, T., Nakai, J., Friedrich, T., Iwabe, N., Miyata, T. & Furuichi, T. (1993) Primary structure and functional expression of the omega-conotoxin-sensitive N-type calcium channel from rabbit brain. *Neuron* 10: 585-598.

Gomora, J.C., Daud, A.N., Weiergraber, M. & Perez-Reyes, E. (2001) Block of cloned human T-type calcium channels by succinimide antiepileptic drugs. *Mol Pharmacol* 60: 1121-1132.

Gould, R.J., Murphy, K.M., Reynolds, I.J. & Snyder, S.H. (1983) Antischizophrenic drugs of the diphenylbutylpiperidine type act as calcium channel antagonists. *Proc Natl Acad Sci USA* 80: 5122-5125

Grantham, C. J. Main, M..J & Cannell, M.B. (1994) Fluspirilene block of N-type calcium current in NGF-differentiated PC12 cells. *Brit J Pharmacol* 111: 483-488.

Hatakeyama, S., Wakamori, M., Ino, M., Miyamoto, N., Takahashi, E., Yoshinaga, T., Sawada, K., Imoto, K., Tanaka, I., Yoshizawa, T., Nishizawa, Y., Mori, Y., Niidome, T. & Shoji, S. (2001) Differential nociceptive responses in mice lacking the alpha(1B) subunit of N-type Ca(2+) channels. *Neuroreport* 12(11): 2423-2427.

Heading, C. (1999) Ziconotide. *Curr Opin CPNS Investigational Drugs* 1: 153-166.

Houtchens, M.K., Richert, J.R., Sami, A. & Rose, J.W. (1997) Open label gabapentin treatment for pain in multiple sclerosis. *Multiple Sclerosis* 3: 250-253.

Huguenard, J.R. (1996) Low-threshold calcium currents in central nervous system neurons. *Annu Rev Physiol* 58: 329-48.

Ino, M., Yoshinaga, T., Wakamori, M., Miyamoto, N., Takahashi, E., Sonoda, J., Kagaya, T., Oki, T., Nagasu, T., Nishizawa, Y., Tanaka, I., Imoto, K., Aizawa, S., Koch, S., Schwartz, A., Niidome, T., Sawada, K. & Mori, Y. (2001) Functional disorders of the sympathetic nervous system in mice lacking the alpha 1B subunit (Cav 2.2) of N-type calcium channels. *Proc Natl Acad Sci USA* 98(9): 5323-5328

Janis, R.J & Triggle, D.J. (1991) In Calcium Channels: Their Properties, Functions, Regulation and Clinical Relevance. CRC Press, London.

Jones, O.T. (2002) Ca2+ channels and epilepsy. *Eur J Pharmacol* 447: 211-225.

Kim, C., Jun, K., Lee, T., Kim, S.S., McEnery, M.W., Chin, H., Kim, H.L., Park, J.M., Kim, D.K., Jung, S.J., Kim, J. & Shin, H. (2001) Altered nociceptive response in mice deficient in the alpha(1B) subunit of the voltage-dependent calcium channel. *Mol Cell Neurosci* 18(2): 235-245.

Kim, D., Song, I. Keum, S., Lee, T., Jeong, M.J., Kim, S.S., McEnery, M.W. & Shin, H.S. (2001) Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking the a1G T-type Ca^{2+} channels. *Neuron* 31: 35-45.

King, V.F., Garcia, M.L., Shevell, J.L., Slaughter, R.S. & Kaczorowski, G.J. (1989) Substituted diphenylbutylpiperidines bind to a unique high affinity site on the L-type calcium channel. Evidence for a fourth site in the cardiac calcium entry blocker receptor complex. *J Biol Chem* 264: 5633-5641.

Laird, M.A. & Gidal, B.E. (2000) Use of Gabapentin in the treatment of neuropathic pain. *Annal Pharmacotherap* 34: 802-807.

Lee, J.H., Daud, A.N., Cribbs, L.L., Lacerda, A.E., Pereverzev, A., Klockner, U., Schneider, T. & Perez-Reyes, E. (1999) Cloning and expression of a novel member of the low voltage-activated T-type calcium channel family. *Journal of Neuroscience* 19: 1912-1921.

Magnus, L. (1999) Nonepileptic uses of Gabapentin. *Epilepsia* 40 (*Suppl* 6): S66-S72.

Malmberg, A.B. & Yaksh, T.L. (1994) Voltage-sensitive calcium channels in spinal nociceptive processing: blockade of N- and P-type channels inhibits formalin-induced nociception. *J Neurosci* 14: 4882-4890.

Mathur, V.S. (2000) Ziconotide: A new pharmacological class of drug for the management of pain. *Seminars in Anesthesia, Perioperative medicine and Pain* 19: 67-75.

McCleskey, E. W. & Schroeder, J.E. (1991) Functional properties of voltage dependent calcium channels. *Cur. Topics Membr* 39: 295-326.

McRory, J.E., Santi, C.M., Hamming, K.S., Mezeyova, J., Sutton, K.G., Baillie, D.L., Stea, A., & Snutch, T.P. (2001) Molecular and functional characterization of a family of rat brain T-type calcium channels. *J Biol Chem* 276: 3999-4011.

Mikami, A., Imoto, K., Tanabe, T., Niidome, T., Mori, Y., Takeshima, H., Narumiya, S. & Numa, S. (1989) Primary structure and functional expression of the cardiac dihydropyridine-sensitive calcium channel. *Nature* 340: 230-233.

Miller, R.J. (1987) Multiple calcium channels and neuronal function. *Science* 235: 46-52.

Mori, Y., Friedrich, T., Kim, M.S., Mikami, A., Nakai, J., Ruth, P., Bosse, E., Hofmann, F., Flockerzi, V. & Furuichi, T. (1991) Primary structure and functional expression from complementary DNA of a brain calcium channel. *Nature* 350: 398-402

Nicholson, B. (2000) Gabapentin use in neuropathic pain syndromes. *Acta Neurol Scand* 101: 359-371.

Penn R.D. & Paice J.A. (2000) Adverse effects associated with the intrathecal administration of ziconotide. *Pain* 85: 291-296.

Perez-Reyes, E. (2003) Molecular physiology of low-voltage-activated T-type calcium channels. *Physiol Rev* 83: 117-161.

Perez-Reyes, E., Cribbs, L.L., Daud, A., Lacerda, A.E., Barclay, J., Williamson, M.P., Fox, M., Rees, M. & Lee J.H. (1998) Molecular characterization of a neuronal low-voltage-activated T-type calcium channel. *Nature* 391: 896-900.

Ridgeway, B., Wallace, M. & Gerayli, A. (2000) Ziconotide for the treatment of severe spasticity after spinal cord injury. *Pain* 85: 287-289.

Rowbotham, M., Harden, N.N., Stacey, B., Podolnick, P. & Magnus-Miller, L. (1998) Gabapentin for the treatment of postherpetic neuralgia: a multicentre, double-blind cross-over study. *JAMA* 280: 1837-1842.

Saegusa, H., Kurhara, T., Zong, S., Minowa, O., Kazuno, A., Han, W., Matsuda, Y., Yamanaka, H., Osanai, M., Noda, T. & Tanabe, T. (2000) Altered pain responses in mice lacking α1E subunit of the voltage dependent Ca channel. *Proc Natl Acad Sci USA* 97: 6132-6137.

Salemme, F.R., Spurlino, J. & Bone, R. (1997) Serendipity meets precision: the integration of structure-based drug design and combinatorial chemistry for efficient drug discovery. *Structure* 5: 319-324

Santi, C.M., Cayabyab, F.S., Sutton, K.G., McRory, J.E., Mezeyova, J., Hamming, K.S., Parker, D., Stea, A., & Snutch, T.P. (2002) Differential inhibition of T-type calcium channels by neuroleptics. *J Neurosci* 22: 396-403.

Sather, W.A., Tanabe, T., Zhang, J.F., Mori, Y., Adams, M.E. & Tsien, R.W. (1993) Distinctive biophysical and pharmacological properties of class A (BI) calcium channel alpha 1 subunits. *Neuron* 11: 291-303.

Sluka, K.A. (1998) Blockade of N- and P/Q-type calcium channels reduces the secondary heat hyperalgesia induced by acute inflammation. *J Pharmacol Exp Ther* 287: 232-237.

Snutch, T.P., Tomlinson, W.J., Leonard, J.P. & Gilbert, M.M. (1991) Distinct calcium channels are generated by alternative splicing and are differentially expressed in the mammalian CNS. *Neuron* 7:45-57

Soong, T.W., Stea, A., Hodson, C.D., Dubel, S.J., Vincent, S.R. & Snutch, T.P. (1993) Structure and functional expression of a member of the low voltage-activated calcium channel family. *Science* 260: 1133-1136

Stea, A., Soong T.W. & Snutch, T.P. (1994) Voltage-gated calcium channels. In: Handbook on Ion Channels. RA North (ed). CRC Press, p. 113-151.

Stea, A., Tomlinson, W.J., Soong, T.W., Bourinet, E., Dubel, S.J., Vincent, S.R. & Snutch, T.P. (1994) Localization and functional properties of a rat brain alpha 1A calcium channel reflect similarities to neuronal Q- and P-type channels. *Proc Natl Acad Sci USA* 91: 10576-10580.

Su, H., Sochivko, D., Becker, A., Chen, J., Jiang, Y., Yaari, Y. & Beck, H. (2002) Upregulation of a T-type Ca^{2+} channel causes a long-lasting modification of neuronal firing mode after status epiletpicus. *J Neurosci* 22: 3645-3655.

Taylor, C.P., Gee, N.S., Su, T.-Z., Kocsis, J.D., Welty, D.F., Brown, J.P., Dooley, D.J., Boden, P. & Singh, L. (1998) A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res* 29: 233-249.

Tomlinson, W.J., Stea, A., Bourinet, E., Charnet, P., Nargeot, J. & Snutch, T.P. (1993) Functional properties of a neuronal class C L-type calcium channel. *Neuropharmacology* 32: 1117-1126

Tumilowicz, J.J., Nichols, W.W., Cholon, J.J. & Greene, A.E. (1970) Definition of a continuous human cell line derived from neuroblastoma. *Cancer Res* 30(8): 2110-2118.

Vanegas, H. & Schaible, H-G. (2000) Effects of antagonists to high-threshold calcium channels upon spinal mechanism of pain, hyperalgesia and allodynia. *Pain* 85: 9-18.

Wang, Y-X., Pettus, M., Philips, C., Gao, D., Bowersox, S.S. & Luther, R.R. (1998) Antinociceptive properties of a selective neuronal N-type calcium channel blocker, ziconotide (SNX-111), in rat model of post-operative pain. *Soc Neurosci Abstr* 24: 1626.

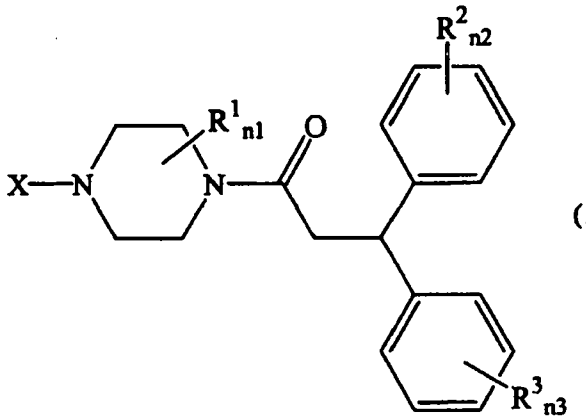
Wentworth, P..Jr., & Janda, K.D. (1998) Generating and analyzing combinatorial chemistry libraries. *Curr Opin Biotechnol* 9: 109-115.

Williams, M.E., Brust, P.F., Feldman, D.H., Patthi, S., Simerson, S., Maroufi, A., McCue, A.F., Velicelebi, G., Ellis, S.B.& Harpold, M.M. (1992) Structure and functional expression of an omega-conotoxin-sensitive human N-type calcium channel. *Science* 257: 389-395.

Williams, M.E., Feldman, D.H., McCue, A.F., Brenner, R., Velicelebi, G., Ellis, S.B. & Harpold, M.M. (1992) Structure and functional expression of alpha 1, alpha 2, and beta subunits of a novel human neuronal calcium channel subtype. *Neuron* 8: 71-84.

Claims

1. A compound of the formula:



(I)

including the salts and conjugates thereof,

wherein each R^1-R^3 is independently a non-interfering substituent; and

wherein a combination of R^2 and R^3 may form a bridge between phenyl groups, which may be a bond or a CR_2 group, an NR group, O, or S wherein the S is optionally oxidized;

n^1 is 0-4 and n^2 and n^3 are independently 0-5; and

wherein X is selected from the group consisting of:

(a) optionally substituted alkyl (1-12C) or optionally substituted alkenyl (2-12C) optionally including one or more N, O or S with the proviso that any N included in a ring is secondary or is tertiary solely because of an alkyl substitution;

(b) optionally substituted aryl, provided that if n^1 is 0, and aryl is phenyl or pyridyl, said aryl must contain at least one substituent and wherein if said aryl is phenyl and contains only one substituent, said substituent must comprise an aryl group or a trialkylsilyl group and wherein said phenyl is not 2,3-dimethylphenyl or fused to an aliphatic ring;

(c) CO-aryl or CRH-aryl wherein R is H, alkyl, or a heteroaromatic ring, wherein when R is H, aryl is optionally substituted 4-pyridyl, or is substituted phenyl (other than phenyl fused to an aliphatic ring) or is substituted naphthyl or is substituted 5-membered aryl; and

(d) alkylene-aryl or alkylene-carbocyclyl wherein said alkylene contains at least 2 C, and further optionally contains one heteroatom and/or is substituted by =O and/or OH provided that if said alkylene is CH_2CH_2, $CH_2CH_2CH_2$, CH_2CH_2O or $CH_2CH_2CH_2O$, and said aryl is phenyl, said phenyl must be substituted; and if said alkylene is $CH_2CH_2CH_2O$ substituted by OH, said aryl is other than substituted quinolyl or monosubstituted phenyl.

2. The compound of claim 1, wherein each R^1-R^3 is independently halo, NO, NO_2, CN, SO_2H, SO_3H, optionally substituted alkyl (1-12C), alkenyl (2-12C), alkynyl (2-12C), aryl (6-12C) or arylalkyl, arylalkenyl or arylalkynyl (each 7-16C) wherein in each of the foregoing 1-4C may be replaced by a heteroatom (Si, N, O and/or S) and wherein said optional substituents may include =O and wherein when alkyl, alkenyl, or alkynyl comprises at least one cyclic moiety, the number of C contained may be up to and including 18, wherein one or more C may be replaced by a heteroatom, and

wherein two substituents at adjacent positions on the same ring may form a 3-7 membered saturated or unsaturated ring fused to said substituted ring, said fused ring is optionally itself substituted and optionally contains one or more heteroatoms (N, S, O), and

wherein R^1 may be keto.

3. The compound of claim 1, wherein X is alkyl (1-12C) or alkenyl (2-12C) optionally including one or more N, O or S with the proviso that any N included in a ring is secondary or is tertiary solely because of an alkyl substitution.

4. The compound of claim 3, wherein X is acyclic.

5. The compound of claim 1, wherein X is aryl, provided that if aryl is phenyl or pyridyl, said aryl must contain at least one substituent and wherein if said aryl is phenyl and contains only one substituent, said substituent must comprise an aryl group or a trialkylsilyl group and wherein said phenyl is not 2,3-dimethylphenyl or fused to an aliphatic ring.

6. The compound of claim 5, wherein X is benzimidazole, benzothiazole, or substituted phenyl.

7. The compound of claim 1, wherein CRH-aryl wherein R is H, alkyl, or a heteroaromatic ring, wherein when R is H, aryl is optionally substituted 4-pyridyl, or is substituted phenyl other than phenyl fused to an aliphatic ring, or is substituted naphthyl or is substituted 5-membered aryl.

8. The compound of claim 7, wherein R is cyclopropyl or a thiophene residue.

9. The compound of claim 1, wherein X is alkylene-aryl wherein said alkylene contains at least 2 C, and further optionally contains one heteroatom and/or is substituted by =O and/or OH provided that if said alkylene is CH_2CH_2, $CH_2CH_2CH_2$, CH_2CH_2O or $CH_2CH_2CH_2O$, and said aryl is phenyl, said phenyl must be substituted; and if said alkylene is $CH_2CH_2CH_2O$ substituted by OH, said aryl is other than substituted quinolyl or monosubstituted phenyl.

10. The compound of claim 9, wherein said alkylene comprises a keto substituent.

11. The compound of claim 9, wherein X is substituted phenyl coupled to $(CH_2)_n$- or $Y(CH_2)_n$, wherein n is 2-5, and Y is NH, O or S.

12. The compound of claim 1, wherein at least one of n1-n3 is 0.

13. The compound of claim 1, wherein n1 is 0 or R^1 is alkyl

14. The compound of claim 1, wherein both n2 and n3 are 0.

15. The compound of claim 1, wherein all of n1-n3 are 0.

16. The compound of claim 1 which is

1-{4-[4-(4-Fluoro-benzyl)-phenyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-[4-(3,5-Di-tert-butyl-4-hydroxy-benzyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-{4-[3-(4-Amino-2,3,5-trimethyl-phenoxy)-2-hydroxy-propyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-(4-Adamantan-1-ylmethyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one;

1-(4-Benzothiazol-2-yl-piperazin-1-yl)-3,3-diphenyl-propan-1-one;

3,3-Diphenyl-1-{4-[2-(3,4,5-trimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-propan-1-one;

1-{4-[2-(3,4-Dimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

N-(2,6-Dimethyl-phenyl)-2-[4-(3,3-diphenyl-propionyl)-piperazin-1-yl]-acetamide;

2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-N-methyl-N-phenyl-acetamide;

3,3-Diphenyl-1-[4-(1-phenyl-ethyl)-piperazin-1-yl]-propan-1-one;

1-[4-(2-Diallylamino-ethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-[4-(2-Dipropylamino-ethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-(4-sec-Butyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one;

1-[4-(1-Ethyl-propyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-[4-(1-Methyl-piperidin-3-ylmethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-(4-Heptyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one;

3,3-Diphenyl-1-(4-pyridin-4-ylmethyl-piperazin-1-yl)-propan-1-one;

1-[4-(3,5-Dichloro-phenyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-(4-Cycloheptyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one;

1-[4-(3,4-Dimethyl-phenyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-(4-Biphenyl-4-yl-piperazin-1-yl)-3,3-diphenyl-propan-1-one;

1-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-[4-(1-Methyl-piperidin-4-ylmethyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

N-{2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-ethyl}-3,4,5-trimethoxy-benzamide;

1-(4-Naphthalen-1-ylmethyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one

1-(4-Isopropyl-piperazin-1-yl)-3,3-diphenyl-propan-1-one;

1-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

3,3-Diphenyl-1-[4-(4-trimethylsilanyl-phenyl)-piperazin-1-yl]-propan-1-one;

3,3-Diphenyl-1-[4-(2-phenylamino-ethyl)-piperazin-1-yl]-propan-1-one;

1-{4-[2-(2,4-Difluoro-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

3,3-Diphenyl-1-{4-[2-(2,3,5,6-tetrafluoro-phenoxy)-ethyl]-piperazin-1-yl}-propan-1-one;

1-[4-(1-Benzyl-1H-benzoimidazol-2-yl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

3,3-Diphenyl-1-[4-(phenyl-thiophen-2-yl-methyl)-piperazin-1-yl]-propan-1-one;

1-{4-[Cyclopropyl-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

(4-{2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-ethoxy}-2,3,6-trimethyl-phenyl)-carbamic acid tert-butyl ester;

1-{4-[2-(4-Amino-2,3,5-trimethyl-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-{4-[2-(4-Methoxy-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-{4-[2-(Benzo[1,3]dioxol-5-yloxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-{4-[2-(2,4-Dichloro-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-{4-[2-(4-Fluoro-phenoxy)-ethyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one; or

3,3-Diphenyl-1-[4-(2-phenylsulfanyl-ethyl)-piperazin-1-yl]-propan-1-one;

1-(3,3-Diphenyl-propionyl)-4-pyridin-4-ylmethyl-piperazine-2-carboxylic acid ethyl ester;

1-(3,3-Diphenyl-propionyl)-4-(1-methyl-pyridin-4-ylmethyl)-piperazine-2-carboxylic acid ethyl ester;

N-{2-[4-(3,3-Diphenyl-propionyl)-piperazin-1-yl]-2-oxo-ethyl}-benzamide;

1-{4-[1-(4-Fluoro-benzyl)-1H-benzoimidazol-2-yl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

1-[4-(4-Fluroro-benzoyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-[4-(1-Methyl-1H-benzoimidazol-2-yl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one;

1-{4-[2-Hydroxy-3-((1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyloxy)-propyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one;

4-3,5-Di-tert-butyl-4-methoxy-benzoyl)-1-(3,3-diphenyl-propionyl)-piperazin-2-one;

or a salt or conjugate thereof.

17. A pharmaceutical composition for use in treating conditions characterized by abnormal calcium channel activity which composition comprises, in admixture with a pharmaceutically acceptable excipient, a dosage amount of at least one compound of claim 1, wherein said conditions are selected from the group consisting of stroke, pain, anxiety disorders, depression, addiction, gastrointestinal disorders, genitourinary disorders, cardiovascular disease, epilepsy, diabetes, and cancer.

18. A method to treat conditions associated with abnormal calcium channel activity in a subject which method comprises administering to a subject in need of such treatment at least one compound of claim 1 or a pharmaceutical composition thereof, wherein said conditions are selected from the group consisting of stroke, pain, anxiety disorders, depression, addiction, gastrointestinal disorders, genitourinary disorders, cardiovascular disease, epilepsy, diabetes, and cancer.

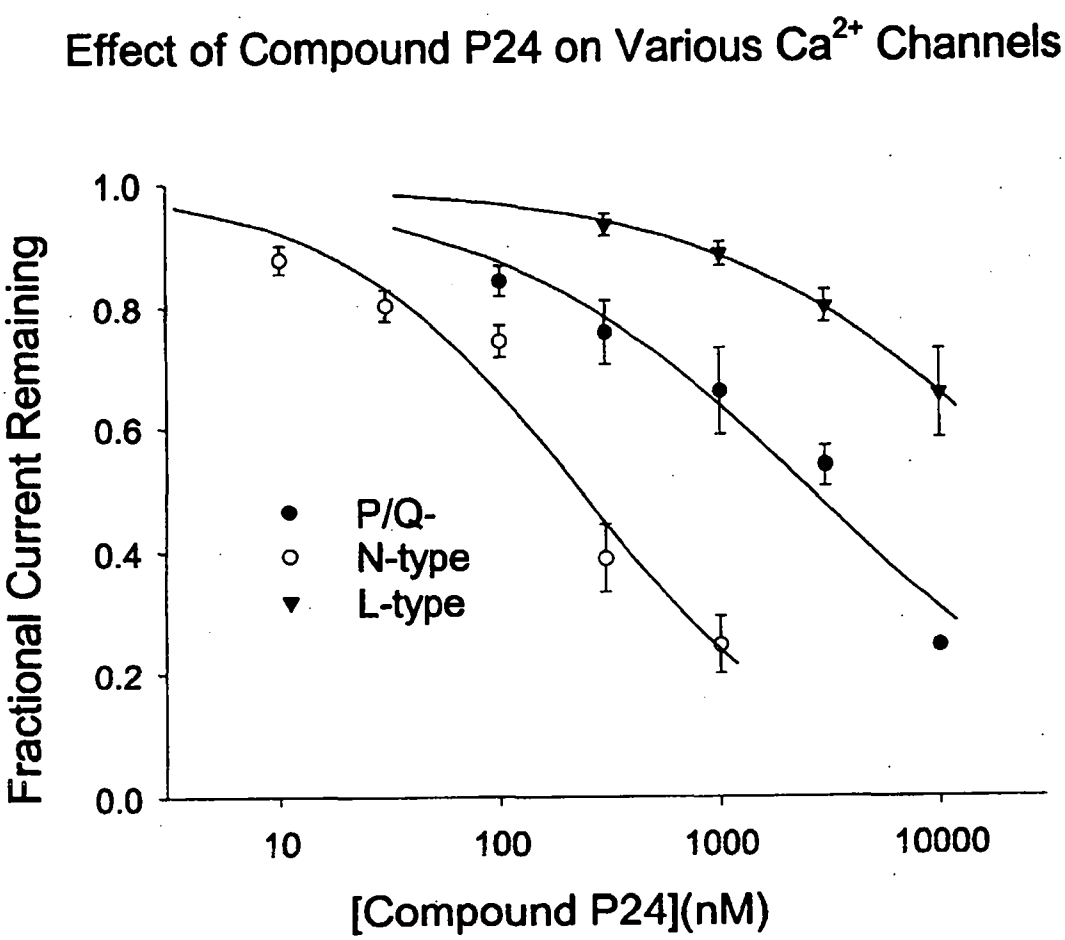
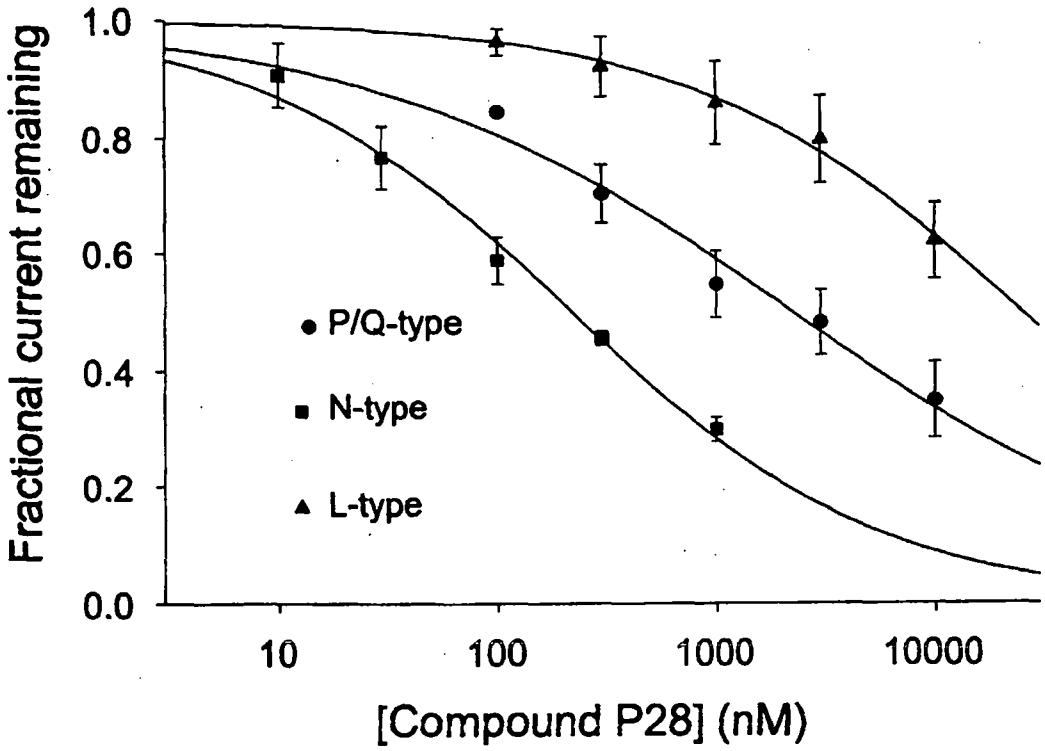

Effect of Compound P24 on Various Ca2+ Channels
Fractional Current Remaining
1.0
0.8
0.6
0.4
0.2
0.0
P/Q-
N-type
L-type
10
100
1000
10000
[Compound P24](nM)

Figure 1

Effect of Compound P28 on Various Ca^{2+} Channels



P/Q-type IC_{50} = 6446 ± 3877 (6) nM

N-type IC_{50} = 214 ± 39 (5) nM

L-type IC_{50} = 19975 ± 7056 (5) nM

Figure 2