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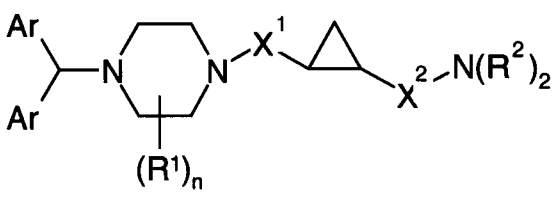
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(54) Title: CYCLOPROPYL-PIPERAZINE COMPOUNDS AS CALCIUM CHANNEL BLOCKERS



(I)

(57) Abstract: Methods and compounds effective in ameliorating conditions characterized by unwanted calcium channel activity, particularly unwanted N-type calcium channel activity are disclosed. Specifically, a series of compounds containing both a piperazine ring and a cyclopropyl ring are disclosed of the general formula (I) where X^1 and X^2 are linkers.

CYCLOPROPYL-PIPERAZINE COMPOUNDS AS CALCIUM CHANNEL BLOCKERS

Technical Field

[0001] The invention relates to compounds useful in treating conditions associated with calcium channel function, and particularly conditions associated with N-type calcium channel activity. More specifically, the invention concerns compounds containing piperazine derivatives and also possessing cyclopropyl functionality that are useful in treatment of conditions such as stroke and pain.

Background Art

[0002] 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, R.J., *Science* (1987) 235:46-52; Augustine, G.J. *et al.*, *Annu Rev Neurosci* (1987) 10: 633-693). 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.

[0003] 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, H. & Schaible, H-G., *Pain* (2000) 85: 9-18). 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) *supra*).

[0004] Two examples of either FDA-approved or investigational drugs 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, C.P. *et al.*, *Epilepsy Res* (1998) 29: 233-249). 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, R.M. & Calcutt, N.A., *Neurosci Lett* (1999) 262: 101-104; Field, M.J. *et al.*, *Pain* (1999) 80: 391-398; Cheng, J-K., *et al.*, *Anesthesiology* (2000) 92: 1126-1131; Nicholson, B., *Acta Neurol Scand* (2000) 101: 359-371).

[0005] While its mechanism of action is not completely 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.

[0006] 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, M. *et al.*, *JAMA* (1998) 280:1831-1836), postherpetic neuralgia (Rowbotham, M. *et al.*, *JAMA* (1998) 280: 1837-1842), trigeminal neuralgia, migraine and pain associated with cancer and multiple sclerosis (Di Trapini, G. *et al.*, *Clin Ter* (2000) 151: 145-148; Caraceni, A. *et al.*, *J Pain & Symp Manag* (1999) 17: 441-445; Houtchens, M.K. *et al.*, *Multiple Sclerosis* (1997) 3: 250-253; see also Magnus, L., *Epilepsia* (1999) 40(Suppl 6): S66-S72; Laird, M.A. & Gidal, B.E., *Annal Pharmacotherap* (2000) 34: 802-807; Nicholson, B., *Acta Neurol Scand* (2000) 101: 359-371).

[0007] 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, A.B. & Yaksh, T.L., *J Neurosci* (1994) 14: 4882-4890; Bowersox, S.S. *et al.*, *J Pharmacol*

Exp Ther (1996) 279: 1243-1249; Sluka, K.A., *J Pharmacol Exp Ther* (1998) 287:232-237; Wang,Y-X. *et al.*, *Soc Neurosci Abstr* (1998) 24: 1626).

[0008] 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, V.S., *Seminars in Anesthesia, Perioperative Medicine and Pain* (2000) 19: 67-75). 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, C., *Curr Opin CPNS Investigational Drugs* (1999) 1: 153-166). 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, B. *et al.*, *Pain* (2000) 85: 287-289). 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.

[0009] U.S. patents 6,011,035; 6,294,533; 6,310,059; , 6,387,897; 6,492,375; 6,943,168; 6,951,862; 6,949,554; 6,997,397; and 7,064,128; 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 ; 10/746,933 filed 23 December 2003; 10/655,393 filed 3 September 2003; 10/821,584 filed 9 April 2004; 10/821,389 filed 9 April 2004; 10/928,564, filed August 27, 2004; 11/214,218 filed August 29, 2005; and 11/215,064 filed August 30, 2005, disclose calcium channel blockers where a piperidine or piperazine ring is substituted by various aromatic moieties.

[0010] 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 benzhydryl 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 benzhydryl 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. U.S. Pat. No. 6,458,781 describes 79 amides as calcium channel antagonists though only a couple of which contain both piperazine rings and benzhydryl moieties. 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 benzhydryl but mandate additional substituents to maintain functionality.

[0011] Certain compounds containing both benzhydryl 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.

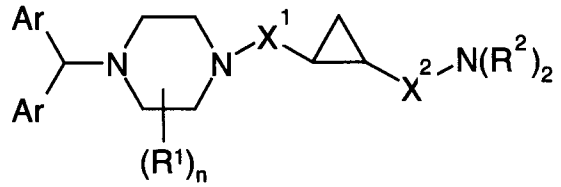
[0012] The present invention provides novel compounds having calcium channel activity, and which are active as inhibitors of N-type calcium channels in particular. These compounds are thus useful for treatment of disorders including pain and certain mood disorders, gastrointestinal disorders, genitourinary disorders, neurologic disorders and metabolic disorders.

[0013] All patents, patent applications and publications identified herein are hereby incorporated by reference in their entirety.

Disclosure of the Invention

[0014] The invention relates to compounds useful in treating conditions modulated by calcium channel activity and in particular conditions mediated by N-type channel activity.

The compounds of the invention are heterocyclic compounds with structural features that enhance the calcium channel blocking activity of the compounds. Thus, in one aspect, the invention is directed to a method of treating conditions mediated by calcium channel activity by administering to patients in need of such treatment at least one compound of formula (1):



(1)

or a pharmaceutically acceptable salt or conjugate thereof, wherein

each X^1 and X^2 is independently an optionally substituted alkylene (1-4C), alkenylene (2-4C), alkynylene (2-4C), heteroalkylene (2-4C), heteroalkenylene (2-4C), or heteroalkynylene (2-4C);

each Ar is independently an optionally substituted aromatic or heteroaromatic ring;

R^1 is =O, =NOR', halo, CN, OR', SR', SOR', SO_2R', NR'_2, NR'(CO)R', or $NR'SO_2R'$, wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), aryl (6-10C), (6-10C)aryl-(1-6C)alkyl, and (5-12C)heteroaryl-(1-6C)alkyl;

or R^1 may be an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C), (C5-C12)heteroaryl-(C1-C6)alkyl, and (C6-C12)aryl-(C1-C6)alkyl;

each R^2 is independently H, or an optionally substituted group selected from alkyl (1-8C), alkenyl (2-8C), alkynyl (2-8C), heteroalkyl (2-8C), heteroalkenyl (2-8C), heteroalkynyl (2-8C), aryl (6-10C), heteroaryl (5-12C), (5-12C)heteroaryl-(C1-C8)alkyl, and (C6-C12)aryl-(C1-C8)alkyl; and wherein both R^2 may together form an optionally substituted heterocyclic or heteroaromatic ring;

n is 0-4; and

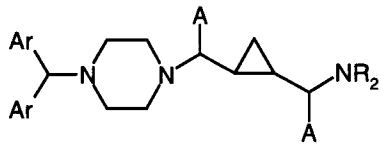
wherein the optional substituents on each Ar, X^1, X^2 and R^2 are independently selected from halo, CN, NO_2, CF_3, OCF_3, COOR', $CONR'_2$, OR', SR', SOR', SO_2R', NR'_2, NR'(CO)R', and $NR'SO_2R'$, wherein each R' is independently H or an optionally

substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), aryl (6-10C), (6-10C)aryl-(1-6C)alkyl, and (5-12C)heteroaryl-(1-6C)alkyl;

or the optional substituents may be one or more optionally substituted groups selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C), (C6-C12)aryl-(C1-C6)alkyl and benzhydryl; and wherein two R' on a single N can cyclize to form a 3-8 membered ring containing up to two heteroatoms selected from N, O and S as ring members;

and wherein the optional substituent on X^1 and X^2 may further be selected from =O and =NOR'.

In a more particular embodiment, the invention provides a compound of formula (2):



(2)

or a pharmaceutically acceptable salt or conjugate thereof, wherein each A is independently H, or =O;

each Ar is independently an optionally substituted phenyl ring; and

each R is independently H, or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), C5-C12-heteroaryl-C1-C6-alkyl, and C6-C12-aryl-C1-C6-alkyl; and wherein both R may together form an optionally substituted heterocyclic or heteroaromatic ring.

[0015] The invention is also directed to compounds of formula (1) or (2) useful to modulate calcium channel activity, particularly N-type channel activity, wherein the definition of such compound is as above. The invention is also directed to the use of these compounds for the preparation of medicaments for the treatment of conditions requiring modulation of calcium channel activity, and in particular N-type calcium channel activity. In another aspect, the invention is directed to pharmaceutical compositions containing these compounds and to the use of these compositions for treating conditions requiring modulation of calcium channel activity, and particularly N-type calcium channel activity.

Detailed Description

[0016] As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight-chain, branched-chain and cyclic monovalent substituents, as well as combinations of these, containing only C and H when unsubstituted. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butynyl, and the like. Typically, the alkyl, alkenyl and alkynyl groups contain 1-8C (alkyl) or 2-8C (alkenyl or alkynyl). In some embodiments, they contain 1-6C, 1-4C or 1-2C (alkyl); or 2-6C or 2-4C (alkenyl or alkynyl). Further, any hydrogen atom on one of these groups can be replaced with a halogen atom, and in particular a fluoro or chloro, and still be within the scope of the definition of alkyl, alkenyl and alkynyl. For example, CF_3 is a 1C alkyl. These groups may be also be substituted by other substituents.

[0017] Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined and contain at least one carbon atom but also contain one or more O, S or N heteroatoms or combinations thereof within the backbone residue whereby each heteroatom in the heteroalkyl, heteroalkenyl or heteroalkynyl group replaces one carbon atom of the alkyl, alkenyl or alkynyl group to which the heteroform corresponds. In preferred embodiments, the heteroalkyl, heteroalkenyl and heteroalkynyl groups have C at each terminus to which the group is attached to other groups, and the heteroatom(s) present are not located at a terminal position. As is understood in the art, these heteroforms do not contain more than three contiguous heteroatoms. In preferred embodiments, the heteroatom is O or N. For greater certainty, to the extent that alkyl is defined as 1-6C, then the corresponding heteroalkyl contains 2-6 C, N, O, or S atoms such that the heteroalkyl contains at least one C atom and at least one heteroatom. Similarly, when alkyl is defined as 1-6C or 1-4C, the heteroform would be 2-6C or 2-4C respectively, wherein one C is replaced by O, N or S. Accordingly, when alkenyl or alkynyl is defined as 2-6C (or 2-4C), then the corresponding heteroform would also contain 2-6 C, N, O, or S atoms (or 2-4) since the heteroalkenyl or heteroalkynyl contains at least one carbon atom and at least one heteroatom. Further, heteroalkyl, heteroalkenyl or heteroalkynyl substituents may also contain one or more carbonyl groups. Examples of heteroalkyl, heteroalkenyl and heteroalkynyl groups include CH_2OCH_3, $CH_2N(CH_3)_2$, CH_2OH, $(CH_2)_nNR_2$, OR, COOR, $CONR_2$, $(CH_2)_n$ OR, $(CH_2)_n$ COR, $(CH_2)_nCOOR$, $(CH_2)_nSR$, $(CH_2)_nSOR$, $(CH_2)_nSO_2R$, $(CH_2)_nCONR_2$, NRCOR, NRCOOR, $OCONR_2$, OCOR and the like wherein the group contains at least one C and the size of the substituent is consistent with the definition of alkyl, alkenyl and alkynyl.

[0018] As used herein, the terms "alkylene," "alkenylene" and "alkynylene" refers to divalent groups having a specified size, typically 1-2C, 1-4C, 1-6C or 1-8C for the saturated groups and 2-4C, 2-6C or 2-8C for the unsaturated groups. They include straight-chain, branched-chain and cyclic forms as well as combinations of these, containing only C and H when unsubstituted. Because they are divalent, they can link together two parts of a molecule, as exemplified by X in formula (1). Examples include methylene, ethylene, propylene, cyclopropan-1,1-diyl, ethylidene, 2-butene-1,4-diyl, and the like. These groups can be substituted by the groups typically suitable as substituents for alkyl, alkenyl and alkynyl groups as set forth herein. Thus C=O is a C1 alkylene that is substituted by =O, for example.

[0019] Heteroalkylene, heteroalkenylene and heteroalkynylene are similarly defined as divalent groups having a specified size, typically 2-4C, 2-6C or 2-8C for the saturated groups and 2-4C, 2-6C or 2-8C for the unsaturated groups. They include straight chain, branched chain and cyclic groups as well as combinations of these, and they further contain at least one carbon atom but also contain one or more O, S or N heteroatoms or combinations thereof within the backbone residue, whereby each heteroatom in the heteroalkylene, heteroalkenylene or heteroalkynylene group replaces one carbon atom of the alkylene, alkenylene or alkynylene group to which the heteroform corresponds. As is understood in the art, these heteroforms do not contain more than three contiguous heteroatoms.

[0020] "Aromatic" moiety or "aryl" moiety refers to any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system and includes a monocyclic or fused bicyclic moiety such as phenyl or naphthyl; "heteroaromatic" or "heteroaryl" also refers to such 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 to be considered aromatic 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. Typically, the ring systems contain 5-12 ring member atoms or 6-10 ring member atoms. In some embodiments, the aromatic or heteroaromatic moiety is a 6-membered aromatic rings system optionally containing 1-2 nitrogen atoms. More particularly, the moiety is an

optionally substituted phenyl, 2-, 3- or 4-pyridyl, indolyl, 2- or 4- pyrimidyl, pyridazinyl, benzothiazolyl or benzimidazolyl. Even more particularly, such moiety is phenyl, pyridyl, or pyrimidyl and even more particularly, it is phenyl.

[0021] "O-aryl" or "O-heteroaryl" refers to aromatic or heteroaromatic systems which are coupled to another residue through an oxygen atom. A typical example of an O-aryl is phenoxy. Similarly, "arylalkyl" refers to aromatic and heteroaromatic systems which are coupled to another residue through a carbon chain, saturated or unsaturated, typically of 1-8C, 1-6C or more particularly 1-4C when saturated or 2-8C, 2-6C or 2-4C when unsaturated, including the heteroforms thereof. For greater certainty, arylalkyl thus includes an aryl or heteroaryl group as defined above connected to an alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl or heteroalkynyl moiety also as defined above. Typical arylalkyls would be an aryl(6-12C)alkyl(1-8C), aryl(6-12C)alkenyl(2-8C), or aryl(6-12C)alkynyl(2-8C), plus the heteroforms. A typical example is phenylmethyl, commonly referred to as benzyl.

[0022] Typical optional substituents on aromatic or heteroaromatic groups include independently halo, CN, NO_2, CF_3, OCF_3, COOR', CONR'$_2$, OR', SR', SOR', SO_2R', NR'$_2$, NR'(CO)R', or NR'SO_2R', wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), aryl (6-10C), (6-10C)aryl-(1-6C)alkyl, and (5-12C)heteroaryl-(1-6C)alkyl; or the substituent may be an optionally substituted group selected from alkyl (1-8C), alkenyl (2-8C), alkynyl (2-8C), heteroalkyl (2-8C), heteroalkenyl (2-8C), heteroalkynyl (2-8C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C) and (C6-C12)aryl-(C1-C8)alkyl or benzhydryl. Some preferred embodiments of R', particularly where R' is part of an optional substituent described as part of another group, include halo, C1-C6 alkyl, and C1-C6 alkoxy.

[0023] Optional substituents on a non-aromatic group, are typically selected from the same list of substituents on aromatic or heteroaromatic groups and may further be selected from =O and =NOR' where R' is similarly defined. For greater certainty, two substituents on the same N or adjacent C can form a 5-7 membered ring which may contain one or two additional heteroatoms selected from N, O and S.

[0024] Halo may be any halogen atom, especially F, Cl, Br, or I, and more particularly it is fluoro or chloro.

[0025] In general, any alkyl, alkenyl, alkynyl, or aryl (including all heteroforms defined above) group 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 substituents on the basic structures above. 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, and is not included. However, alkyl substituted by aryl, amino, halo and the like would be included.

[0026] R^1 is similarly defined as independently being selected from =O, =NOR', halo, CN, OR', SR', SOR', SO_2R', NR'_2, NR'(CO)R', or NR'SO_2R', wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), and aryl (6-10C); or R^1, R^2 or R^3 may be an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C) and C6-C12-aryl-C1-C6-alkyl. There may be from 0-4 substituents (defined as R^1) on the central piperazine ring and more particularly 0-2 substituents or 0-1 substituents. In certain embodiments, at least one R^1 can be alkyl (C1-C6) or aryl (C6-C12), particularly phenyl.

[0027] Ar is defined as an optionally substituted aromatic or heteroaromatic ring. The two Ar groups may be the same or different; in some embodiments they are the same. In certain embodiments each Ar represent phenyl, so Ar_2CH- represents a benzhydryl, and each phenyl ring may independently be substituted or unsubstituted. In other embodiments, Ar_2CH represents an unsubstituted benzhydryl.

[0028] X^1 and X^2 may independently be an optionally substituted alkylene (1-4C), alkenylene (2-4C), alkynylene (2-4C), heteroalkylene (2-4C), heteroalkenylene (2-4C), or heteroalkynylene (2-4C). In a more particular embodiment, X^1 and X^2 may independently be an optionally substituted 1-2C alkylene, and more particularly an optionally substituted methylene. In even more particular embodiments, X^1 and X^2 may independently be CH_2 or C=O.

[0029] Each R^2 may independently be H, or an optionally substituted group selected from alkyl (1-8C), alkenyl (2-8C), alkynyl (2-8C), heteroalkyl (2-8C), heteroalkenyl (2-8C), heteroalkynyl (2-8C), aryl (6-10C), heteroaryl (5-12C), C5-C12-heteroaryl-C1-C8-alkyl, and

C6-C12-aryl-C1-C8-alkyl. For greater certainty, both R^2 may together form an optionally substituted heterocyclic or heteroaromatic ring.

[0030] In some preferred embodiments, two or more of the particularly described groups are combined into one compound: it is often suitable to combine one of the specified embodiments of one feature as described above with a specified embodiment or embodiments of one or more other features as described above. For example, a specified embodiment includes X^1 as C=O, and another specified embodiment has both Ar as optionally substituted phenyl groups (i.e., an optionally substituted benzhydryl). Thus one preferred embodiment combines both of these features together, i.e., X^1 is CO in combination with both Ar representing optionally substituted benzhydryl. In some specific embodiments, n is 0 and in others n is 1. Thus additional preferred embodiments include n = 0 in combination with any of the preferred combinations set forth above; other preferred combinations include n = 1 in combination with any of the preferred combinations set forth above.

[0031] The compounds of the invention may have ionizable groups so as to be capable of preparation as 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. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

[0032] In some cases, the compounds of the invention contain one or more chiral centers. The invention includes each of the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity, including racemic mixtures. It also encompasses the various diastereomers and tautomers that can be formed. It expressly includes both the cis and trans isomers of the cyclopropane rings shown in Formula (1) and (2), although in some embodiments, the trans cyclopropanes are preferred.

[0033] Compounds of formula (1) and (2) are also useful for the manufacture of a medicament useful to treat conditions characterized by undesired N-type calcium channel activities.

[0034] In addition, the compounds of the invention may be coupled through conjugation to substances designed to alter the pharmacokinetics, for targeting, or for other reasons. Thus, the invention further includes conjugates of these compounds. For example, polyethylene glycol is often coupled to substances to enhance half-life; the compounds may be coupled to liposomes covalently or noncovalently or to other particulate carriers. They may also be coupled to targeting agents such as antibodies or peptidomimetics, often through linker moieties. Thus, the invention is also directed to the compounds of formula (1) and (2) when modified so as to be included in a conjugate of this type.

Modes of Carrying out the Invention

[0035] The compounds of formula (1) and (2) are useful in the methods of the invention and exert their desirable effects through their ability to modulate the activity of calcium channels, particularly the activity of N-type calcium channels. This makes them useful for treatment of certain conditions where modulation of N-type calcium channels is desired, including: chronic and acute pain; mood disorders such as anxiety, depression, and addiction; neurodegenerative disorders; gastrointestinal disorders such as inflammatory bowel disease and irritable bowel syndrome; genitourinary disorders such as urinary incontinence, interstitial colitis and sexual dysfunction; neuroprotection such as cerebral ischemia, stroke and traumatic brain injury; and metabolic disorders such as diabetes and obesity.

[0036] Acute pain as used herein includes but is not limited to nociceptive pain and post-operative pain. Chronic pain includes but is not limited by: peripheral neuropathic pain such as post-herpetic neuralgia, diabetic neuropathic pain, neuropathic cancer pain, failed back-surgery syndrome, trigeminal neuralgia, and phantom limb pain; central neuropathic pain such as multiple sclerosis related pain, Parkinson disease related pain, post-stroke pain, post-traumatic spinal cord injury pain, and pain in dementia; musculoskeletal pain such as osteoarthritic pain and fibromyalgia syndrome; inflammatory pain such as rheumatoid arthritis and endometriosis; headache such as migraine, cluster headache, tension headache syndrome, facial pain, headache caused by other diseases; visceral pain such as interstitial cystitis, irritable bowel syndrome and chronic pelvic pain syndrome; and mixed pain such as lower back pain, neck and shoulder pain, burning mouth syndrome and complex regional pain syndrome.

[0037] Anxiety as used herein includes but is not limited to the following conditions: generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive disorder, and post-traumatic stress syndrome. Addiction includes but is not limited to dependence, withdrawal and/or relapse of cocaine, opioid, alcohol and nicotine.

[0038] Neurodegenerative disorders as used herein include Parkinson's disease, Alzheimer's disease, multiple sclerosis, neuropathies, Huntington's disease and amyotrophic lateral sclerosis (ALS).

[0039] For greater certainty, in treating osteoarthritic pain, joint mobility will also improve as the underlying chronic pain is reduced. Thus, use of compounds of the present invention to treat osteoarthritic pain inherently includes use of such compounds to improve joint mobility in patients suffering from osteoarthritis.

[0040] 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 receptors are most useful in these conditions. Many of the members of the genus of compounds of formula (1) and (2) exhibit high affinity for N-type channels. Thus, as described below, they are screened for their ability to interact with N-type channels as an initial indication of desirable function. It is particularly desirable that the compounds exhibit IC_{50} values of <1 μM. The IC_{50} is the concentration which inhibits 50% of the calcium, barium or other permeant divalent cation flux at a particular applied potential.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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 in Examples 3 and 4.

Libraries and Screening

[0046] The compounds of the invention can be synthesized individually using methods known in the art *per se*, or as members of a combinatorial library.

[0047] 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, *e.g.*, the N-type channel. In addition, using standard screening protocols, the libraries may be screened for compounds that block additional channels or receptors such as sodium channels, potassium channels and the like.

[0048] 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, barium or other permeant divalent cation 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.

[0049] 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.

[0050] 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.

[0051] 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 or as resting channel blockers. 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. Finally, resting channel blockers would diminish the peak current amplitude during the very first depolarization after drug application without additional inhibition during the depolarization.

[0052] Accordingly, a library of compounds of formula (1) or formula (2) can be used to identify a compound having a desired combination of activities that includes activity against at least one type of calcium channel. For example, the library can be used to identify a compound having a suitable level of activity on N-type calcium channels while having minimal activity on HERG K+ channels.

Utility and Administration

[0053] 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.

[0054] In general, for use in treatment, the compounds of formula (1) or (2) may be used alone, as mixtures of two or more compounds of formula (1) and/or (2) or in combination with other pharmaceuticals. An example of other potential pharmaceuticals to combine with the compounds of formula (1) and (2) would include pharmaceuticals for the treatment of the same indication but having a different mechanism of action from N-type calcium channel blocking. For example, in the treatment of pain, a compound of formula (1) or (2) may be combined with another pain relief treatment such as an NSAID, or a compound which selectively inhibits COX-2, or an opioid, or an adjuvant analgesic such as an antidepressant. Another example of a potential pharmaceutical to combine with the compounds of formula (1) or (2) would include pharmaceuticals for the treatment of different yet associated or

related symptoms or indications. Depending on the mode of administration, the compounds will be formulated into suitable compositions to permit facile delivery.

[0055] The compounds of the invention may be prepared and used as pharmaceutical compositions comprising an effective amount of at least one compound of formula (1) or (2) admixed with a pharmaceutically acceptable carrier or excipient, as is well known in the art. 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.

[0056] 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.

[0057] Various sustained release systems for drugs have also been devised. See, for example, U.S. patent No. 5,624,677.

[0058] 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 is understood in the art.

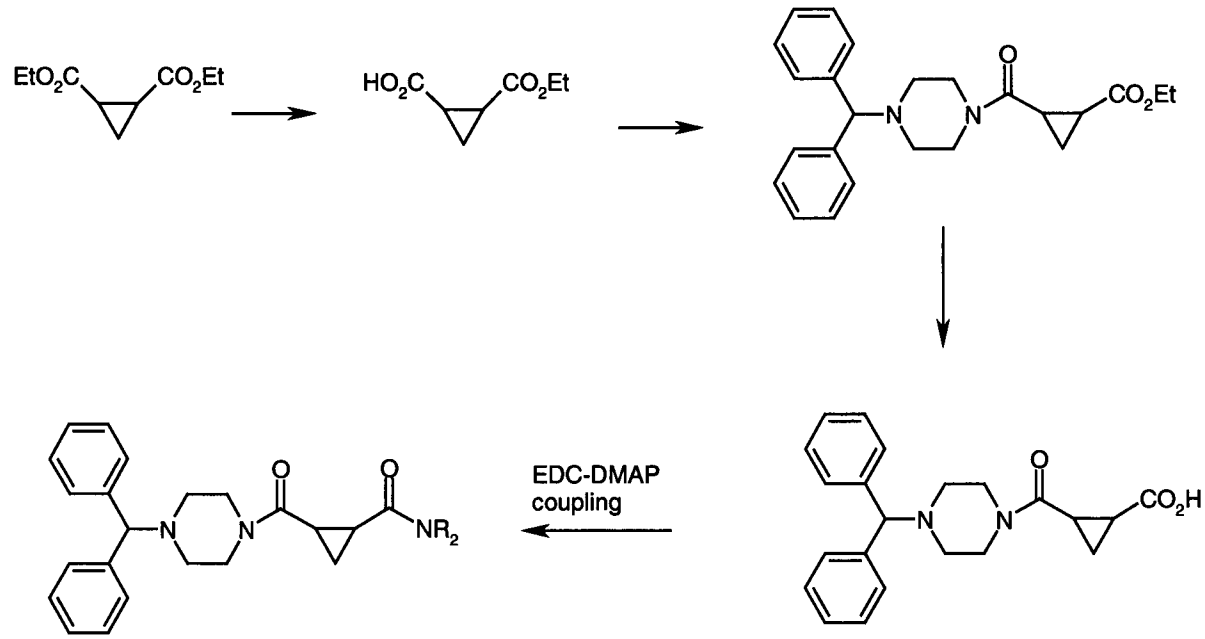
[0059] For administration to animal or human subjects, the dosage of the compounds of the invention is typically 0.01-15 mg/kg, preferably 0.1-10 mg/kg. However, dosage levels are highly dependent on the nature of the condition, drug efficacy, the condition of the patient, the judgment of the practitioner, and the frequency and mode of administration. Optimization of the dosage for a particular subject is within the ordinary level of skill in the art.

Synthesis of the Invention Compounds

[0060] The following reaction schemes and examples are intended to illustrate the synthesis of a representative number of compounds. Accordingly, the following examples

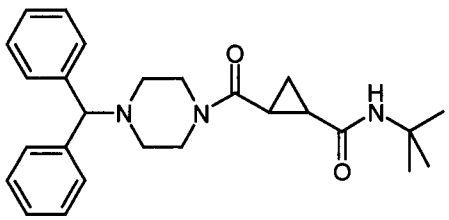
are intended to illustrate but not to limit the invention. Additional compounds not specifically exemplified may be synthesized using conventional methods in combination with the methods described hereinbelow.

Reaction Scheme 1



Example 1

Synthesis of (1R,2R)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropanecarboxamide



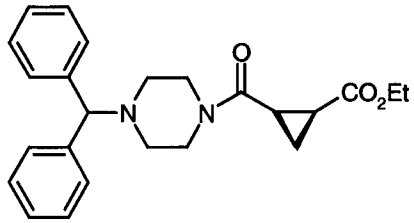
A. Synthesis of (1R,2R)-2-(ethoxycarbonyl)cyclopropanecarboxylic acid



[0061] Diethyl (1R, 2R)-1,2-cyclopropanedicarboxylate 3.5ml (20mmol) and NaOH (0.8g, 20.4mmol) in EtOH (60ml) and water (5ml) was stirred at room temperature overnight. The mixture was then concentrated to remove the solvent. The residue was redissolved in water and washed with diethyl ether (40ml) to remove any unreacted starting material. The aqueous solution was then adjusted to pH~2 with 2N HCl and extracted with

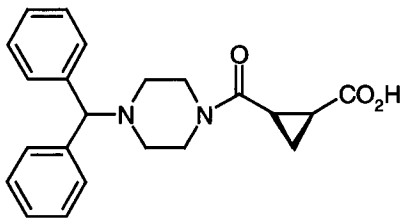
ethyl acetate (2x40ml). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to give crude monoester monoacid (2.8g, 90%).

B. Synthesis of (1R,2R)-ethyl 2-(4-benzhydrylpiperazine-1-carbonyl)cyclopropanecarboxylate



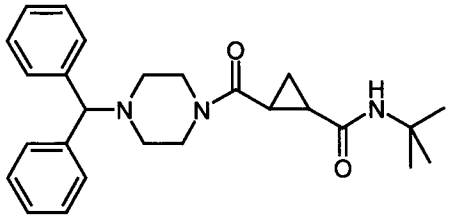
[0062] A solution of (1R,2R)-2-(ethoxycarbonyl)cyclopropanecarboxylic acid (1.1g, 7mmol), 1-(diphenylmethyl)-piperazine (1.7g, 7mmol), N,N-diisopropyl-N-ethyl amine (DIEA, 3ml) and HATU (*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide, 3.2g, 8.4mmol) in 15ml dichloromethane (DCM) was stirred at room temperature overnight. DCM solution was washed with satd. sodium bicarbonate (40ml) and dried over sodium sulfate and concentrated. The residue was applied to flash column chromatography using petroleum ether and ethyl acetate (7:3) as eluents to give (1R,2R)-ethyl-2-(4-benzhydrylpiperazine-1-carbonyl)cyclopropanecarboxylate (2.15g, 78%).

C. Synthesis of (1R,2R)- 2-(4-benzhydrylpiperazine-1-carbonyl)cyclopropanecarboxylic acid



[0063] (1R,2R)-ethyl-2-(4-benzhydrylpiperazine-1-carbonyl)cyclopropanecarboxylate (2.15g, 5.8mmol) was dissolved in a mixture of THF (30ml), methanol (10ml) and water (10ml) followed by the addition of lithium hydroxide 0.72g (17.4mmol). The mixture was stirred at room temperature overnight, concentrated to remove solvent, neutralized with 2N HCl to pH~3, and the reaction product was extracted with ethyl acetate (40ml). The organic layer was dried over sodium sulfate and concentrated to give (1R,2R)- 2-(4-benzhydrylpiperazine-1-carbonyl)cyclopropanecarboxylic acid (1.82g, 86%).

D. Synthesis of (1R,2R)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropane carboxamide



[0064] A solution of (1R,2R)- 2-(4-benzhydrylpiperazine-1-carbonyl) cyclopropanecarboxyllic acid (0.150g, 0.42mmol), *tert*-butylamine (0.3 g, 0.42mmol), ethyl dimethylaminopropyl carbodiimide (EDC, 0.160g, 0.84mmol) and 4-dimethylaminopyridine (DMAP, trace) in 4ml dichloromethane was stirred at room temperature overnight, concentrated, added water and extracted with ethyl acetate (2x25ml). The combined organic solution was dried over sodium sulfate and concentrated. The residue was applied to flash column chromatography using petroleum ether and ethyl acetate (1:1) as eluents to give (1R,2R)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-tert-butylcyclopropanecarboxamide (90%).

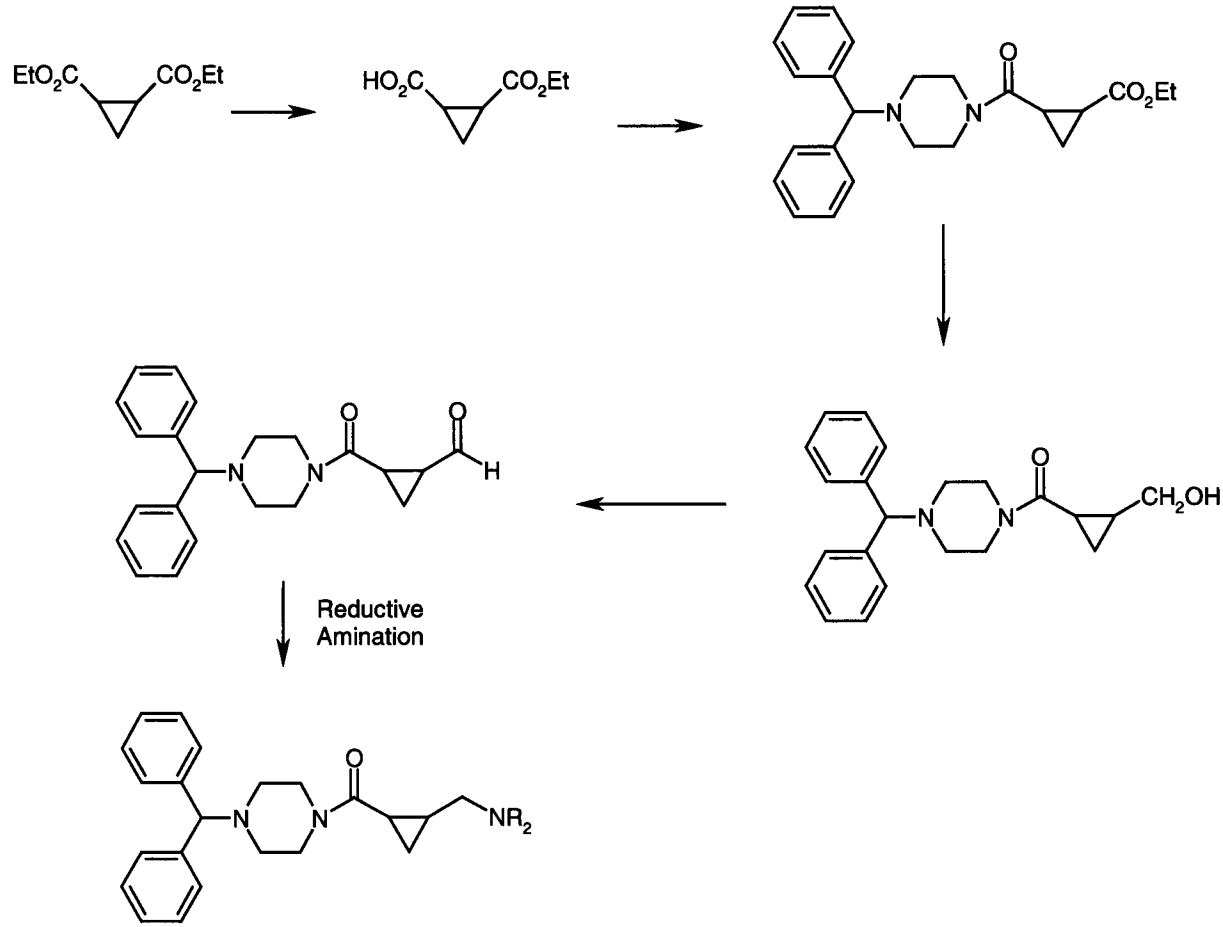
Examples 2-8

[0065] Compound Nos. 17-22 were prepared according to the method of Example 1, and the following yields were obtained as shown in Table 1. The structures for these compounds are shown in Table 3.

Table 1

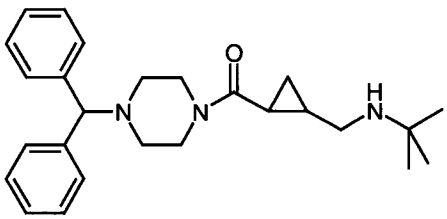
Cmpd. No.	Yield
17	82
18	53
19	57
20	48
21	90
22	57
23	95

Reaction Scheme 2

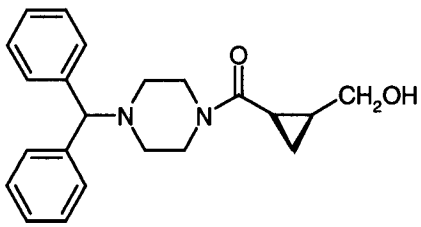


Example 9

Synthesis of (1R,2R)-(4-benzhydrylpiperazin-1-yl)(2-((tert-butylamino)methyl)cyclopropyl)methanone

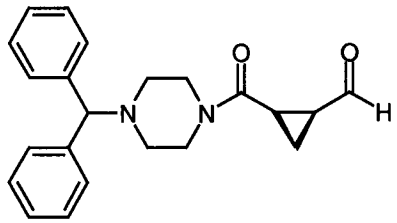


A. Synthesis of (1R,2R)- (4-benzhydrylpiperazin-1-yl)(2-(hydroxymethyl)-cyclopropyl)methanone



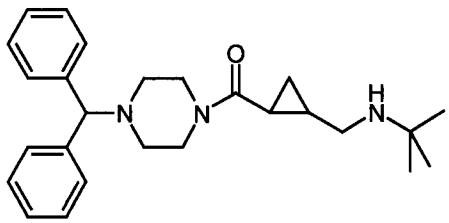
[0066] To a solution of (1R,2R)-ethyl 2-(4-benzhydrylpiperazine-1-carbonyl)cyclopropanecarboxylate (synthesized according to Example 1b, 1.9g, 5mmol) in THF (40 ml) and methanol (2 ml), $LiBH_4$ (0.132g, 6mmol) was added. The resulting mixture was stirred at room temperature overnight. The mixture was then quenched with saturated sodium bicarbonate and extracted with ethyl acetate (3x25ml). The combined organic solution was dried and concentrated to yield the (1R,2R)- (4-benzhydrylpiperazin-1-yl)(2-(hydroxymethyl)-cyclopropyl)methanone product (0.770g, 44%) with the recovery of 0.9 g of the starting material.

B. Synthesis of (1R,2R)- 2-(4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarbaldehyde



[0067] Oxalyl chloride (0.250 ml, 2.87mmol) in 5ml of DCM was cooled to -78°C, followed by the addition of dimethyl sulfoxide (DMSO, 0.465ml, pre-solvated in 1ml of DCM). The solutions were stirred at -78°C for about 15 min. (1R,2R)- (4-benzhydrylpiperazin-1-yl)(2-(hydroxymethyl)cyclopropyl)methanone (0.87g, 2.5 mmol) in DCM (5 ml) was then added and the reaction mixture was stirred further for 30 min. triethylamine (TEA, 1.75ml) was then added and the reaction mixture was allowed to come to room temperature with stirring continued for further 30 min. Water (3 ml) was finally added to quench the reaction and the organic layer was separated, dried over anhydrous sodium sulfate and concentrated to yield the (1R,2R)- 2-(4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarbaldehyde (0.7g crude, 80%).

C. Synthesis of (1R,2R)-(4-benzhydrylpiperazin-1-yl)(2-((tert-butylamino)methyl) cyclopropyl)methanone



[0068] (1R,2R)- 2-(4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarbaldehyde (0.150g, 0.45mmol) and tert-butylamine (0.33g, 0.45mmol) were dissolved in dichloroethane (DCE, 5 ml) and stirred at room temperature. Sodium triacetoxyborohydride (0.150g, 0.675mmol) was added and the reaction mixture was stirred overnight. The reaction was then diluted with DCM (15 ml) and washed with $NaHCO_3$ saturated solution (5ml). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography (5% MeOH/DCM) to give (1R,2R)-(4-benzhydrylpiperazin-1-yl)(2-((tert-butylamino)methyl)cyclopropyl)methanone as a colourless oil (yield 44%).

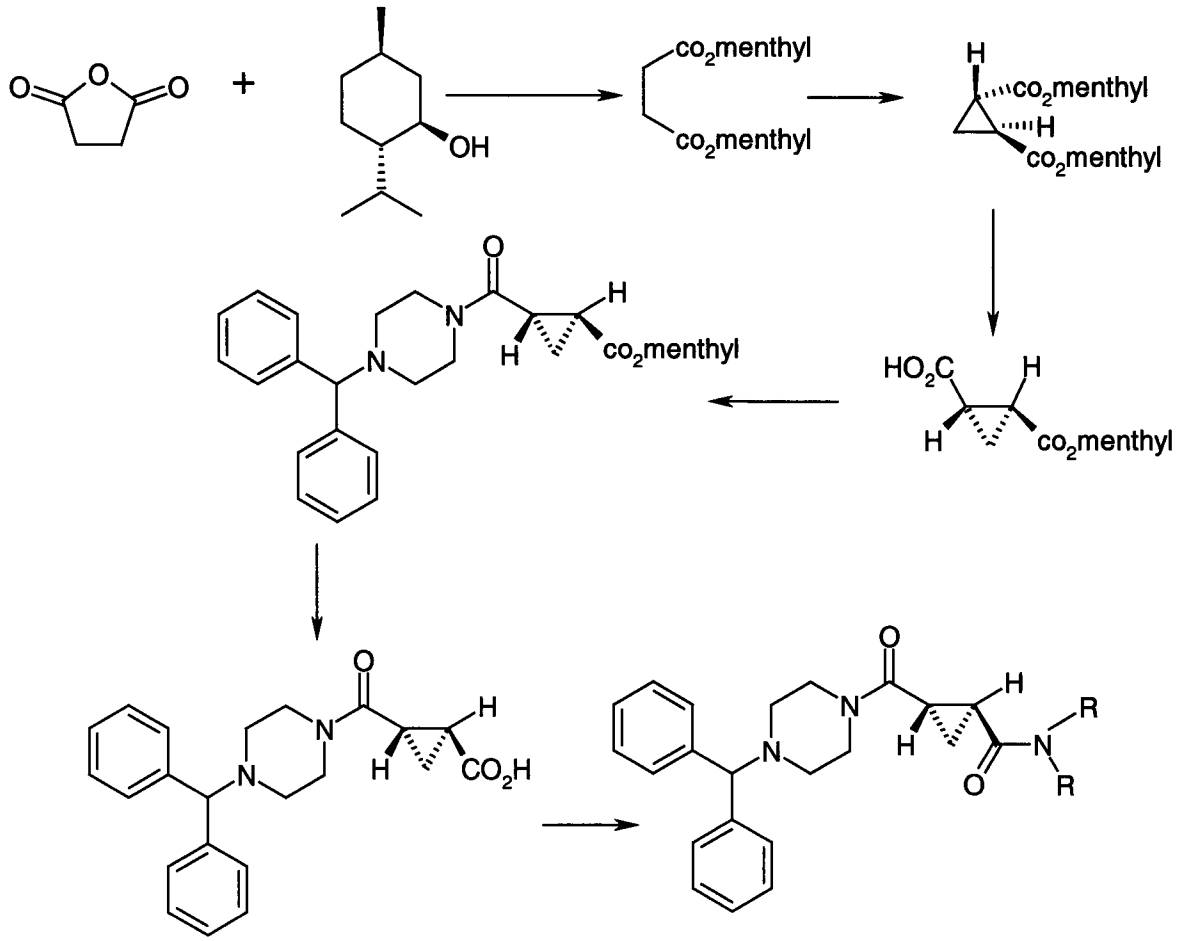
Examples 10-13

[0069] Compound Nos. 42-45 were prepared according to the method of Example 9 and the following yields were obtained as shown in Table 2. The structures for these compounds are shown in Table 3.

Table 2

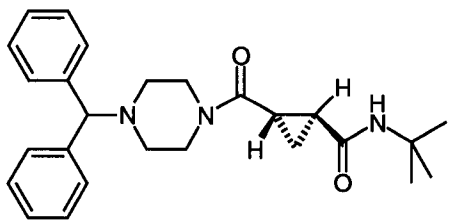
Cmpd. No.	Yield
42	22
43	45
44	44
45	84

Reaction Scheme 3

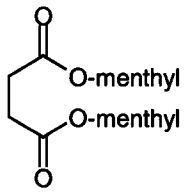


Example 14

Synthesis of (1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-tert-butylcyclopropanecarboxamide (compound 26)

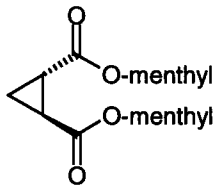


A. Synthesis of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl succinate



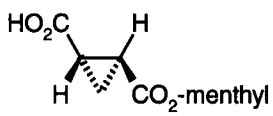
[0070] Succinic anhydride (10g), (1R,2S,5R)-(-) menthol (32g,), 200mg of p-toluenesulfonic acid and 100ml of toluene were refluxed overnight using a Dean Stark trap. The mixture was cooled and diluted with 100ml hexane and poured into 150ml of saturated sodium bicarbonate, methanol (70ml) and water (100ml). The organic phase was separated and the aqueous phase was extracted with hexane (2x) and the combined organic layers were washed with brine and dried. 50 ml methanol was added and left in the refrigerator overnight. The following day, the precipitate was collected to give 30g of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl succinate .

B. Synthesis of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 2- (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl) cyclopropane-1,2-dicarboxylate



[0071] To a cooled solution of 2,2,6,6-tetramethylpiperidine (15ml) in dry THF (100ml), 40ml of n-butyllithium was added dropwise over 10 minutes. The mixture was then cooled to -78°C followed by addition of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl succinate (15g) over 10 min and then 2.2 ml of bromochloromethane was added dropwise over a period of 10 min. The mixture was stirred for two hours and then 1.5 ml of isobutyraldehyde was added to quench the unreacted anion and the reaction mixture was then stirred for an additional 30 min. The reaction mixture was poured onto 1N HCl and the reaction product was extracted with ether (3x100ml), washed with brine and then dried. Column chromatography (18:1-hexane-ether) was used to give of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 2- (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)-cyclopropane-1,2-dicarboxylate in 85% yield.

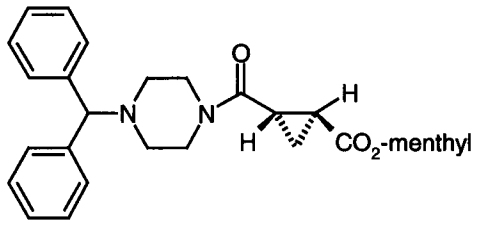
C. Synthesis of (1S,2S)-2-(((1S,2S,5R)-2-isopropyl-5-methylcyclohexyloxy) carbonyl) cyclopropanecarboxylic acid



[0072] (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 2- (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl) cyclopropane-1,2-dicarboxylate (1.5 g), NaOH (160mg), water (0.8ml),

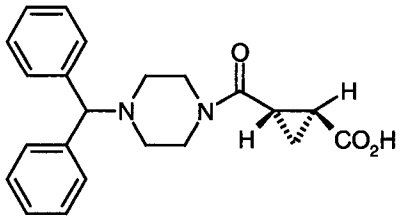
isopropyl alcohol (10ml) were combined and stirred at 50°C overnight and then stirred at 85°C for 2 hr. The reaction mixture was then concentrated and the reaction product was extracted with ether and 5 ml water. The aqueous layer was acidified with 2 N HCl and extracted with ether (3x40) and dried to give the desired product in 90% yield.

D. Synthesis of (1S,2S)-((1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)2-((4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarboxylate



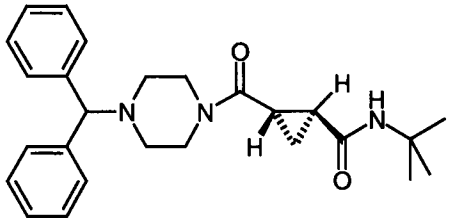
[0073] A solution of (1S,2S)-2-(((1S,2S,5R)-2-isopropyl-5-methylcyclohexyloxy) carbonyl) cyclopropanecarboxylic acid (1.6g), diphenylmethyl piperazine (1.5g), EDC (1.7g) and DMAP (trace) in dichloromethane (20ml) was stirred at room temperature overnight, and then concentrated. Water was added to the reaction mixture and the reaction product was then extracted with ethyl acetate (2x25ml). The combined organic solution was dried over sodium sulfate and concentrated. The residue was applied to flash column chromatography using petroleum ether and ethyl acetate (1:1) as eluents to give (1S,2S)-((1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)2-((4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarboxylate in 76% yield.

E. Synthesis of (1S,2S)-2-(4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarboxylic acid



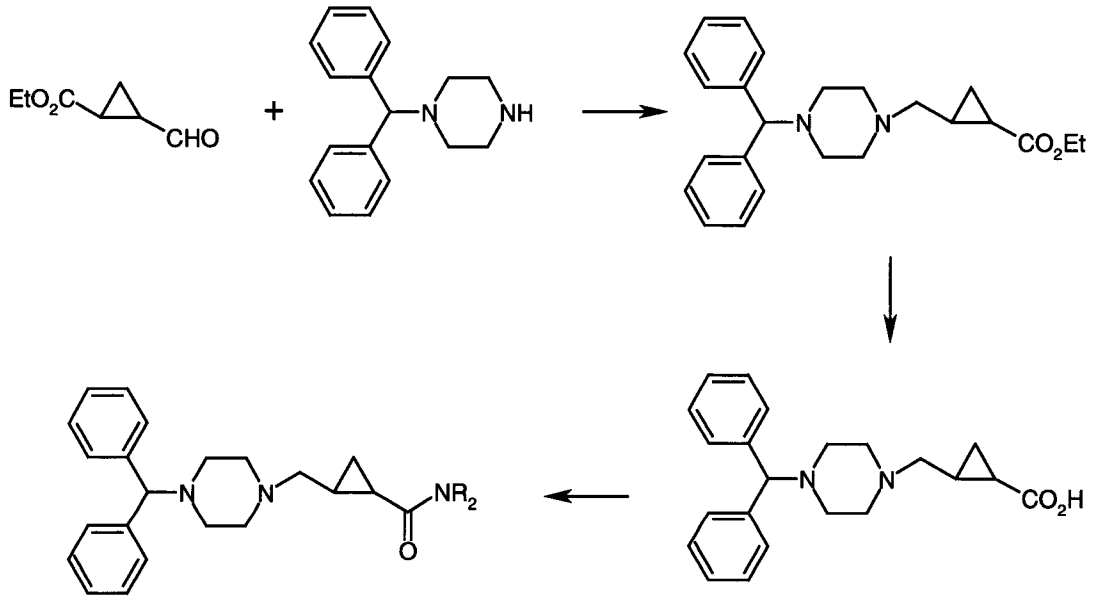
[0074] A solution of (1S,2S)-((1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)2-((4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarboxylate (2.2 g), $LiOH-H_2O$ (1g) , THF (15ml) was heated at 60°C for 5 hr. The reaction mixture was then evaporated. Water (10ml) was added to the reaction mixture and the reaction product was extracted with ether (2x20ml) and then the aqueous phase was acidified with 6N HCl to pH 4.5 and the precipitate was filtered and dried in vacuum to give the desired carboxylic acid in 90% yield.

F. Synthesis of (1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-tert-butylcyclopropanecarboxamide



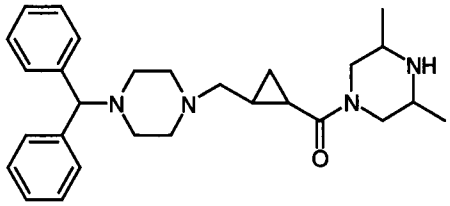
[0075] A solution of (1S,2S)-2-(4-benzhydrylpiperazin-1-carbonyl)cyclopropanecarboxylic acid (100mg, 0.27mmol), tert-butylamine (22mg, 0.3mmol) , HATU (180mg) and 0.2ml of triethylamine in DCM (2ml) was stirred at room temperature overnight. The residue was applied to flash column chromatography using petroleum ether and ethyl acetate (1:1) as eluents to give (1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-tert-butylcyclopropanecarboxamide (90%).

Reaction Scheme 4

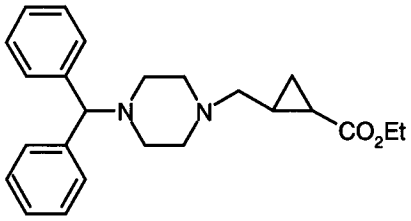


Example 15

Synthesis of (2-(4-benzhydrylpiperazine-1-carbonyl)-2-[(3,5-dimethylpiperazin-1-yl)methyl]cyclopropanecarboxamide (compound 49)

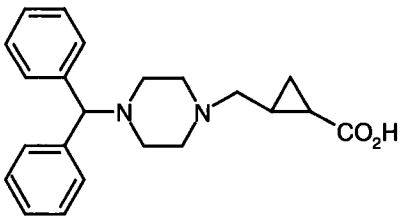


A. Synthesis of ethyl 2-{[4-(diphenylmethyl)piperazin-1yl]methyl}cyclopropanecarboxylate



[0076] Ethyl 2-formyl-1-cyclopropanecarboxylate (4.5 g), diphenylmethylpiperazine (8.5 g) and triacetoxysodium borohydride (9.5) g in dichloroethane (100 ml) was stirred overnight. The solvent was then evaporated and the residue was dissolved in ethyl acetate (100ml) followed by washing with sodium bicarbonate. The organic layer was dried over sodium sulfate and evaporated. The residue was applied to column chromatography using ethyl acetate as eluents to give ethyl 2-{[4-(diphenylmethyl)piperazin-1-yl]methyl}cyclopropanecarboxylate in 92% yield.

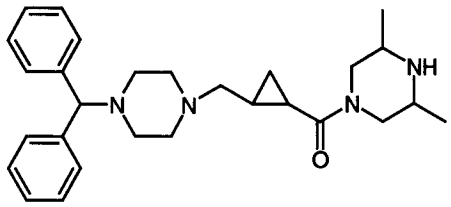
B. Synthesis of 2-{[4-(diphenylmethyl)piperazin-1-yl]methyl}cyclopropanecarboxylic acid



[0077] A solution of ethyl 2-{[4-(diphenylmethyl)piperazin-1-yl]methyl}-cyclopropanecarboxylate (12 g), LiOH-H_20 (10g), water (30ml), THF (100ml), methanol (15ml) was stirred overnight at room temperature. The reaction mixture was evaporated and the residue was then redissolved in water (40 ml) and acidified with 6N HCl to pH 5. The

aqueous layer was then extracted with ethyl acetate to give 10g of 2-{[4-(diphenylmethyl)piperazin-1-yl]methyl}cyclopropanecarboxylic acid in 95% yield.

C. Synthesis of (2-(4-benzhydrylpiperazine-1-carbonyl)-2-[(3,5-dimethylpiperazin-1-yl)methyl]cyclopropanecarboxamide

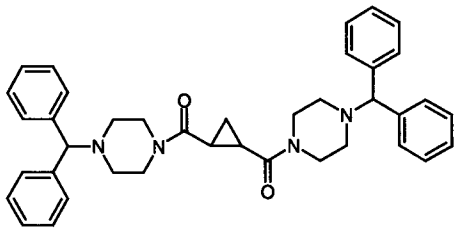
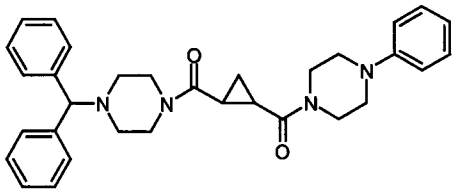
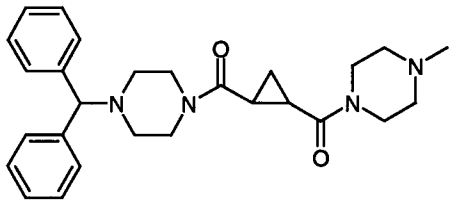
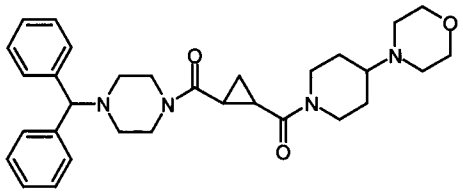
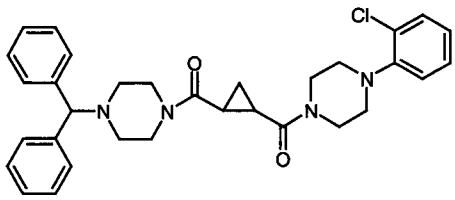
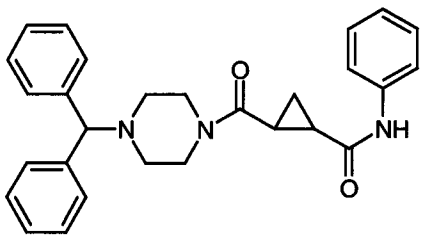


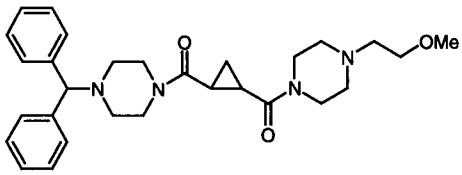
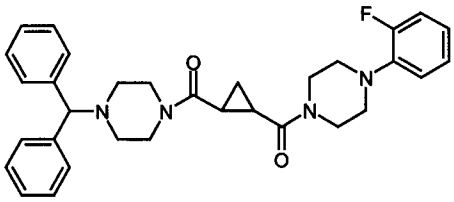
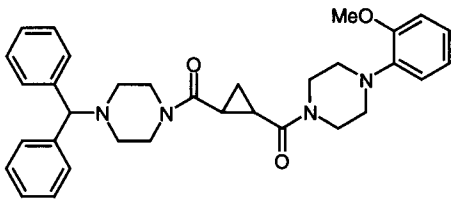
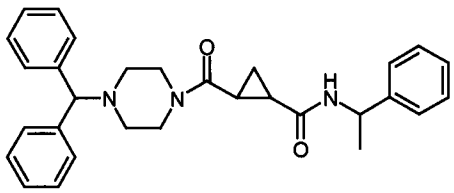
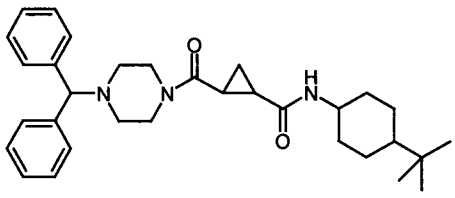
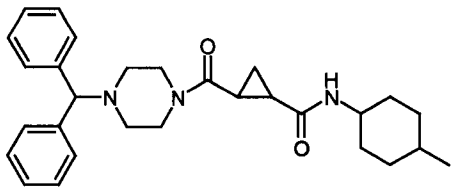
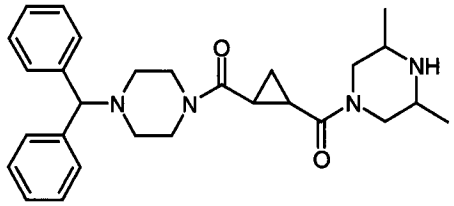
[0078] A solution of 2-{[4-(diphenylmethyl)piperazin-1-yl]methyl}-cyclopropanecarboxylic acid (0.150g, 0.29mmol), 2,6-dimethylpiperazine (33mg, 0.29mmol), EDC (110mg, 0.58mmol) and DMAP (trace) in 4ml dichloromethane was stirred at room temperature overnight. The reaction mixture was then concentrated, water was added and the reaction product was extracted with ethyl acetate (2x25ml). The combined organic solution was dried over sodium sulfate and concentrated. The residue was applied to flash column chromatography using petroleum ether and ethyl acetate (1:1) to give (2-(4-benzhydrylpiperazine-1-carbonyl)-2-[(3,5-dimethylpiperazin-1-yl)methyl]cyclopropanecarboxamide in 70% yield.

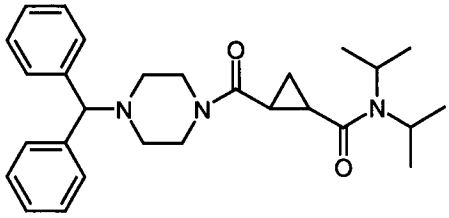
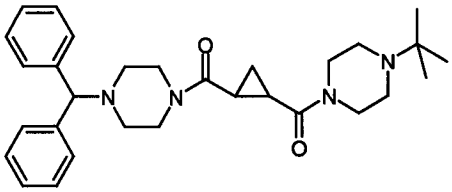
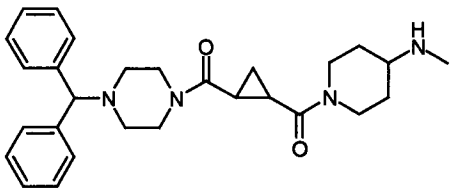
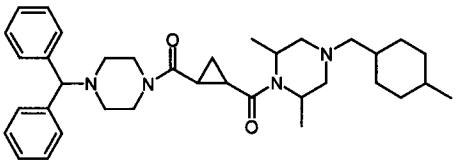
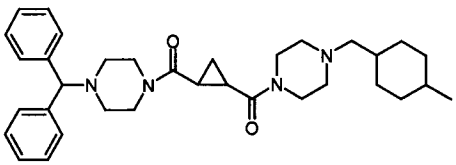
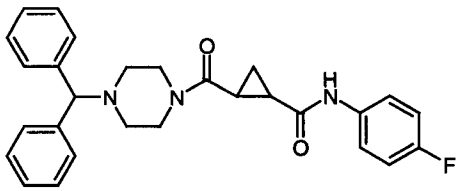
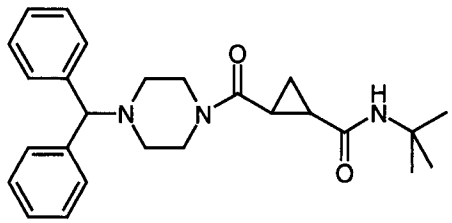
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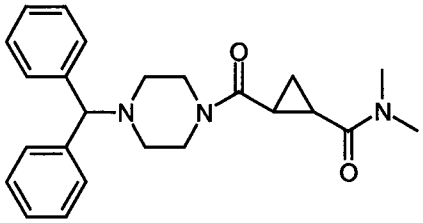
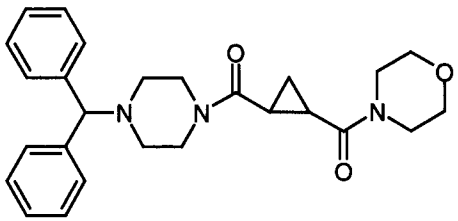
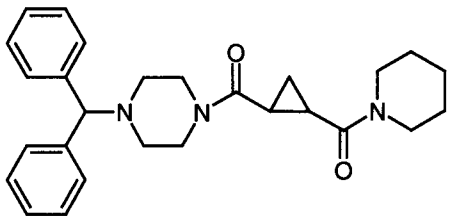
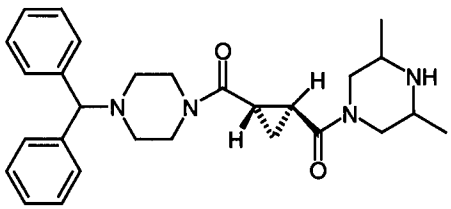
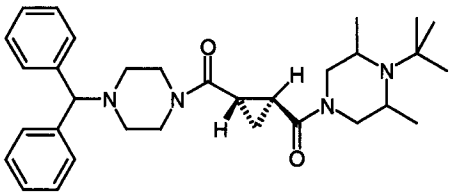
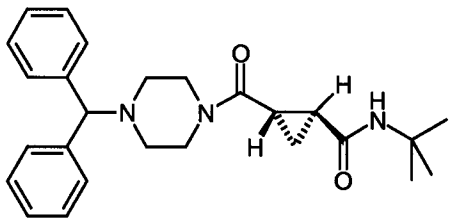
[0079] Following the general procedures set forth in Reaction Schemes 1-4 and Examples 1-15, the following compounds listed in Table 3 below were prepared. Mass spectrometry was employed with the final compound and at various stages throughout the synthesis as a confirmation of the identity of the product obtained (M+1). For the mass spectrometric analysis, samples were prepared at an approximate concentration of 1 μg/mL in acetonitrile with 0.1% formic acid. Samples were then manually infused into an Applied Biosystems API3000 triple quadrupole mass spectrometer and scanned in Q1 in the range of 50 to 700 m/z.

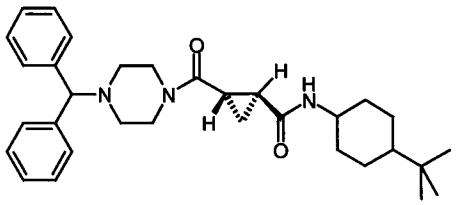
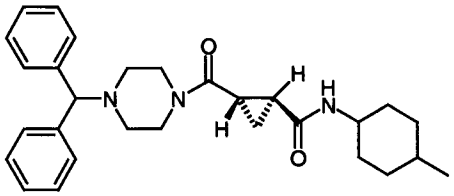
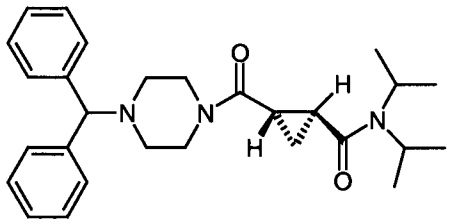
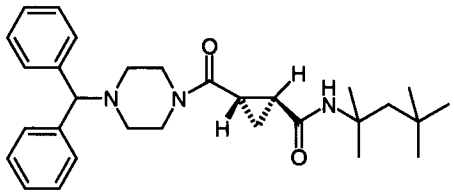
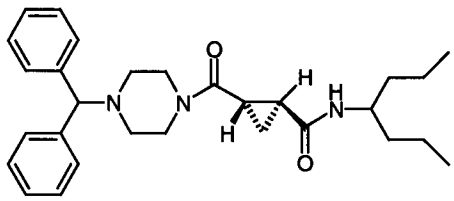
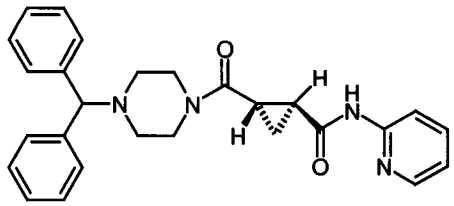
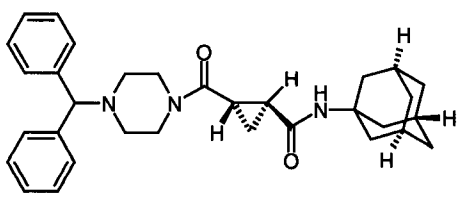
Table 3

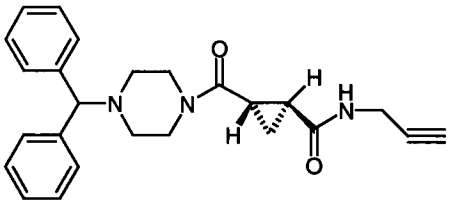
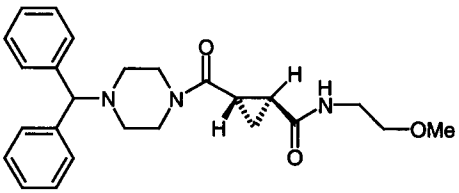
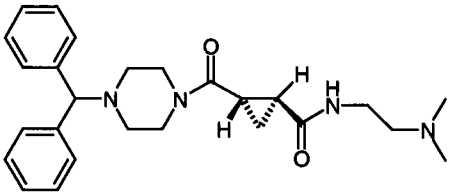
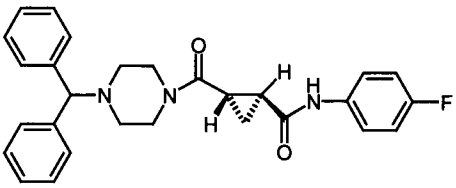
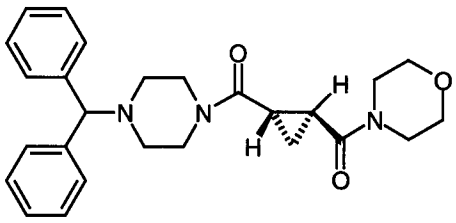
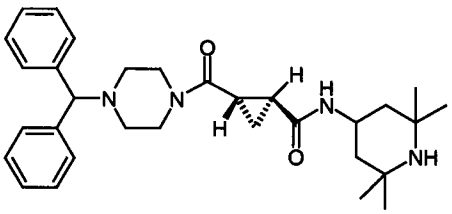
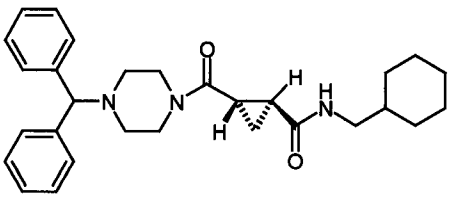
Cmpd No.	Name	Structure	Mass Spec (m/z)
1	Cyclopropane-1,2-diylbis((4-benzhydrylpiperazin-1-yl)methanone)		599.5
2	(4-benzhydrylpiperazin-1-yl)(2-(4-phenylpiperazine-1-carbonyl)cyclopropyl)methanone		509.4
3	(4-benzhydrylpiperazin-1-yl)(2-(4-methylpiperazine-1-carbonyl)cyclopropyl)methanone		447.4
4	(4-benzhydrylpiperazin-1-yl)(2-(4-morpholinopiperadine-1-carbonyl)cyclopropyl)methanone		517.4
5	(4-benzhydrylpiperazin-1-yl)(2-(4-(2-chlorophenyl)piperazine-1-carbonyl)cyclopropyl)methanone		543.4
6	2-(4-benzhydrylpiperazine-1-carbonyl)-N-phenylcyclopropanecarboxamide		440.5

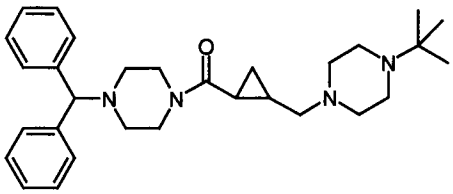
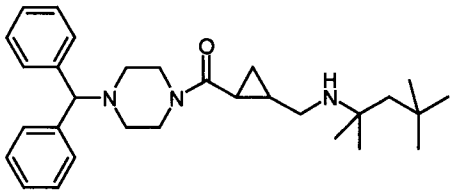
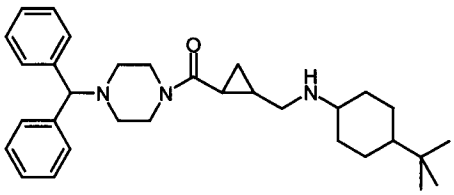
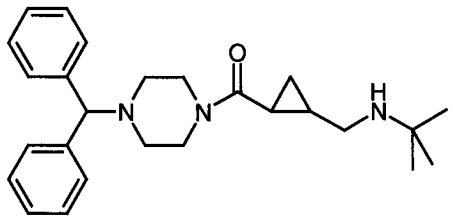
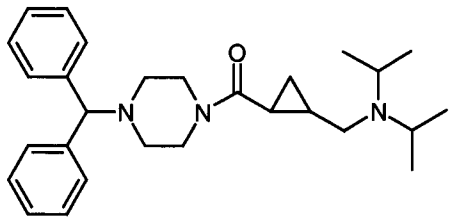
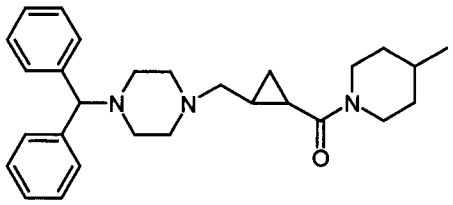
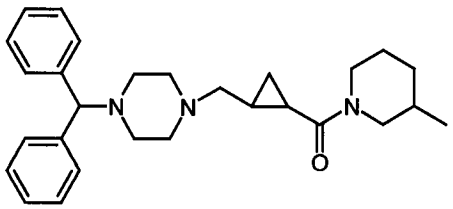
Cmpd No.	Name	Structure	Mass Spec (m/z)
7	(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyethyl)piperazine-1-carbonyl)cyclopropyl)methanone		491.4
8	(4-benzhydrylpiperazin-1-yl)(2-(4-(2-fluorophenyl)piperazine-1-carbonyl)cyclopropyl)methanone		527.5
9	(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyphenyl)piperazine-1-carbonyl)cyclopropyl)methanone		539.5
10	2-(4-benzhydrylpiperazine-1-carbonyl)-N-(1-phenylethyl)cyclopropane carboxamide		468.4
11	2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl)cyclopropane carboxamide		502.4
12	2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl)cyclopropane carboxamide		460.3
13	(4-benzhydrylpiperazin-1-yl)(2-(3,5-dimethylpiperazine-1-carbonyl)cyclopropyl)methanone		461.3

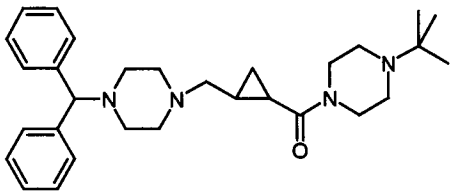
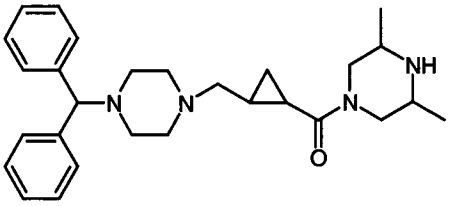
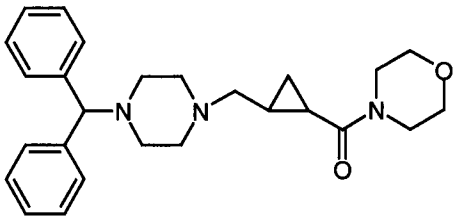
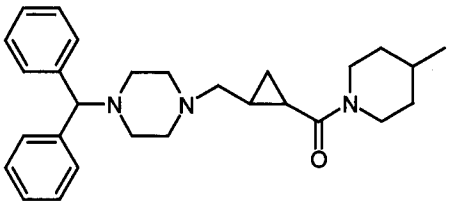
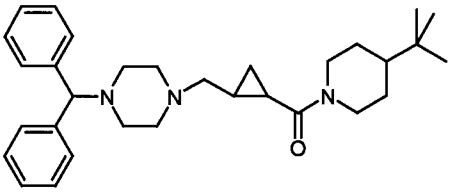
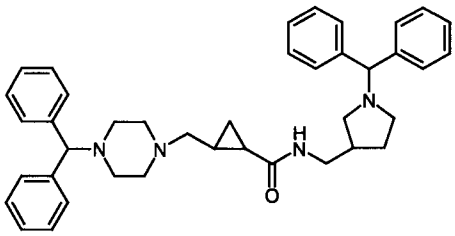
Cmpd No.	Name	Structure	Mass Spec (m/z)
14	2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropylcyclopropane carboxamide		448.4
15	(4-benzhydrylpiperazin-1-yl)(2-(4-tert-butylpiperazine-1-carbonyl)cyclopropyl) methanone		489.5
16	(4-benzhydrylpiperazin-1-yl)(2-(4-(methylamino)piperadine-1-carbonyl)cyclopropyl) methanone		461.3
17	(4-benzhydrylpiperazin-1-yl)(2-(2,6-dimethyl-4-((4-methylcyclohexyl) methyl)piperazine-1-carbonyl) cyclopropyl)methanone		571.5
18	(4-benzhydrylpiperazin-1-yl)(2-(4-((4-methylcyclohexyl)methyl)piperazine-1-carbonyl)cyclopropyl) methanone		543.4
19	2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-fluorophenyl)cyclopropane carboxamide		458.2
20	2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropane carboxamide		420.4

Cmpd No.	Name	Structure	Mass Spec (m/z)
21	2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-dimethylcyclopropanecarboxamide		392.3
22	(4-benzhydrylpiperazin-1-yl)(2-(morpholine-4-carbonyl)cyclopropyl) methanone		434.3
23	(4-benzhydrylpiperazin-1-yl)(2-(piperidine-1-carbonyl)cyclopropyl) methanone		432.3
24	(4-benzhydrylpiperazin-1-yl)((1S,2S)-2-(3,5-dimethylpiperazine-1-carbonyl)cyclopropyl)methanone		461.4
25	(4-benzhydrylpiperazin-1-yl)((1S,2S)-2-(4-*tert*-butyl-3,5-dimethylpiperazine-1-carbonyl)cyclopropyl)methanone		489.4
26	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropanecarboxamide		420.3

Cmpd No.	Name	Structure	Mass Spec (m/z)
27	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl) cyclopropanecarboxamide		502.5
28	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl) cyclopropanecarboxamide		460.3
29	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropyl cyclopropanecarboxamide		448.4
30	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2,4,4-trimethylpentan-2-yl)cyclopropanecarboxamide		476.5
31	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(heptan-4-yl) cyclopropanecarboxamide		462.5
32	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(pyridine-2-yl) cyclopropanecarboxamide		441.4
33	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(adamantyl) cyclopropanecarboxamide		498.5

Cmpd No.	Name	Structure	Mass Spec (m/z)
34	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(prop-2-ynyl) cyclopropanecarboxamide		402.3
35	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2-methoxyethyl) cyclopropanecarboxamide		422.3
36	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2-(dimethylamino)ethyl) cyclopropanecarboxamide		435.4
37	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-fluorophenyl) cyclopropanecarboxamide		458.3
38	(4-benzhydrylpiperazin-1-yl)((1S,2S)-2-(morpholine-4-carbonyl)cyclopropyl) methanone		434.3
39	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2,2,6,6-tetramethyl piperidin-4-yl)cyclopropanecarboxamide		503.5
40	(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(cyclohexylmethyl) cyclopropanecarboxamide		460.4

Cmpd No.	Name	Structure	Mass Spec (m/z)
41	(4-benzhydrylpiperazin-1-yl)(2-(4-*tert*-butylpiperazin-1-yl)methyl)cyclopropyl) methanone		475.4
42	(4-benzhydrylpiperazin-1-yl)(2-((2,44-trimethylpentan-2ylamino)methyl) cyclopropyl)methanone		462.5
43	(4-benzhydrylpiperazin-1-yl)(2-((4-*tert*-butylcyclohexylamino)methyl) cyclopropyl)methanone		488.5
44	(4-benzhydrylpiperazin-1-yl)(2-((*tert*-butylamino)methyl)cyclopropyl) methanone		406.4
45	(4-benzhydrylpiperazin-1-yl)(2-((diisopropylamino)methyl)cyclopropyl) methanone		448.5
46	(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(4-methylpiperidin-1-yl)methanone		432.4
47	(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(3-methylpiperidin-1-yl)methanone		432.3

Cmpd No.	Name	Structure	Mass Spec (m/z)
48	(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(4-tert-butylpiperazin-1-yl)methanone		475.5
49	(2-(4-benzhydrylpiperazine-1-carbonyl)-2-[(3,5-dimethylpiperazin-1-yl)methyl]cyclopropanecarboxamide		447.5
50	(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(morpholino) methanone		420.4
51	(2-((4-benzhydrylpiperazin-1-yl)methyl) cyclopropyl)(4-methylpiperidin-1-yl) methanone		446.4
52	(2-((4-benzhydrylpiperazin-1-yl)methyl) cyclopropyl)(4-*tert*-butylpiperidin-1-yl) methanone		488.5
53	(2-((4-benzhydrylpiperazin-1-yl)methyl)-N-((1-benzhydrylpyrrolidin-3-yl)methyl)cyclopropanecarboxamide		599.6

Example 17

N-type Channel Blocking Activities of Various Invention Compounds

A. Transformation of HEK cells

[0080] 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 (α_{1B} +$\alpha_2\delta$ +β_{1b} cDNA subunits). Alternatively, N-type calcium channels (α_{1B} +$\alpha_2\delta$ +β_{1b} cDNA subunits), L-type channels (α_{1C} +$\alpha_2\delta$ +β_{1b} cDNA subunits) and P/Q-type channels (α_{1A} +$\alpha_2\delta$ +β_{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 cDNA's. Fresh DMEM was supplied and the cells transferred to 28°C/5% CO_2. Cells were incubated for 1 to 2 days prior to whole cell recording.

B. Measurement of Inhibition

[0081] Whole cell patch clamp experiments were performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, Calif.) linked to a personal computer equipped with pCLAMP software. The external and internal recording solutions contained, respectively, 5 mM $BaCl_2$, 10 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 (0.067 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).

[0082] Specific data obtained for N-type channels are shown in Table 4 below.

Table 4

N-type Calcium Channel Block

Compound	IC_{50} @ 0.067Hz (μM)	IC_{50} @ 0.2Hz (μM)
1	0.16	0.15
2	0.44	0.31
3	2.50	1.50
4	>5.83	>3.95
6	3.20	1.90
7	2.00	1.50
8	0.94	0.53
9	0.63	0.43
10	1.55	0.97
11	0.09	0.08
12	0.18	0.12
13	0.71	0.44
14	1.56	0.86
15	8.53	6.86
16	12.54	6.79
18	0.69	0.44

Example 18

Activity of Invention Compounds in Formalin-Induced Pain Model

[0083] The effects of intrathecally delivered compounds of the invention on the rat formalin model can also be measured. The compounds can be reconstituted to stock solutions of approximately 10 mg/ml in propylene glycol. Typically eight Holtzman male rats of 275-375 g size are randomly selected per test article.

[0084] The following study groups can be used, with test article, vehicle control (propylene glycol) and saline delivered intraperitoneally (IP):

Table 5

Formalin Model Dose Groups

Test/Control Article	Dose	Route	Rats per group
Compound	30 mg/kg	IP	6
Propylene glycol	N/A	IP	4
Saline	N/A	IP	7

N/A = Not Applicable

[0085] Prior to initiation of drug delivery baseline behavioral and testing data can be taken. At selected times after infusion of the Test or Control Article these data can then be again collected.

[0086] On the morning of testing, a small metal band (0.5 g) is loosely placed around the right hind paw. The rat is placed in a cylindrical Plexiglas chamber for adaptation a minimum of 30 minutes. Test Article or Vehicle Control Article is administered 10 minutes prior to formalin injection (50 µl of 5% formalin) into the dorsal surface of the right hindpaw of the rat. The animal is then placed into the chamber of the automated formalin apparatus where movement of the formalin injected paw is monitored and the number of paw flinches tallied by minute over the next 60 minutes (Malmberg, A.B., *et al., Anesthesiology* (1993) 79:270-281).

[0087] Results can be presented as Maximum Possible Effect ± SEM, where saline control = 100%.

Example 19

Spinal Nerve Ligation Model of Neuropathic Pain

[0088] Spinal nerve ligation (SNL) injury can be induced using the procedure of Kim and Chung, (Kim, S.H., *et al., Pain* (1992) 50:355-363) in male Sprague-Dawley rats (Harlan; Indianapolis, IN) weighing 200 to 300 grams. Anesthesia is induced with 2% halothane in O_2 at 2 L/min and maintained with 0.5% halothane in O_2. After surgical preparation of the rats and exposure of the dorsal vertebral column from L_4 to S_2, the L_5 and L_6 spinal nerves are tightly ligated distal to the dorsal root ganglion using 4-0 silk suture. The incision is closed, and the animals are allowed to recover for 5 days. Rats that exhibit motor deficiency (such as paw-dragging) or failure to exhibit subsequent tactile allodynia are excluded from

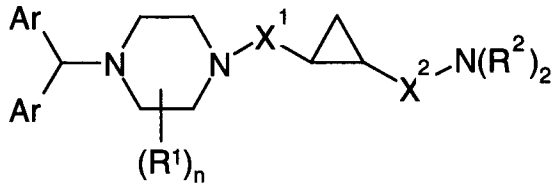
further testing. Sham control rats undergo the same operation and handling as the experimental animals, but without SNL.

[0089] The assessment of tactile allodynia consists of measuring the withdrawal threshold of the paw ipsilateral to the site of nerve injury in response to probing with a series of calibrated von Frey filaments. Each filament is applied perpendicularly to the plantar surface of the ligated paw of rats kept in suspended wire-mesh cages. Measurements are taken before and after administration of drug or vehicle. Withdrawal threshold is determined by sequentially increasing and decreasing the stimulus strength ("up and down" method), analyzed using a Dixon non-parametric test (Chaplan S.R., *et al.*, *J Pharmacol Exp Ther* (1994) 269:1117-1123), and expressed as the mean withdrawal threshold.

[0090] The method of Hargreaves and colleagues (Hargreaves, K., *et al.*, *Pain* (1988) 32:77-8) can be employed to assess paw-withdrawal latency to a thermal nociceptive stimulus. Rats are allowed to acclimate within a plexiglas enclosure on a clear glass plate maintained at 30°C. A radiant heat source (*i.e.*, high intensity projector lamp) is then activated with a timer and focused onto the plantar surface of the affected paw of nerve-injured or carrageenan-injected rats. Paw-withdrawal latency can be determined by a photocell that halted both lamp and timer when the paw is withdrawn. The latency to withdrawal of the paw from the radiant heat source is determined prior to carrageenan or L5/L5 SNL, 3 hours after carrageenan or 7 days after L5/L6 SNL but before drug and after drug administration. A maximal cut-off of 40 seconds is employed to prevent tissue damage. Paw withdrawal latencies can be thus determined to the nearest 0.1 second. Reversal of thermal hyperalgesia is indicated by a return of the paw withdrawal latencies to the pre-treatment baseline latencies (*i.e.*, 21 seconds). Anti-nociception is indicated by a significant ($p < 0.05$) increase in paw withdrawal latency above this baseline. Data is converted to % anti hyperalgesia or % anti-nociception by the formula: (100 x (test latency - baseline latency)/(cut-off - baseline latency) where cut-off is 21 seconds for determining anti-hyperalgesia and 40 seconds for determining anti-nociception.

Claims

1. A method to treat a condition modulated by calcium ion channel activity, which method comprises administering to a subject in need of such treatment an amount of the compound of formula (1) effective to ameliorate said condition, wherein said compound is of the formula:



(1)

or a pharmaceutically acceptable salt or conjugate thereof, wherein

each X^1 and X^2 is independently an optionally substituted alkylene (1-4C), alkenylene (2-4C), alkynylene (2-4C), heteroalkylene (2-4C), heteroalkenylene (2-4C), or heteroalkynylene (2-4C);

each Ar is independently an optionally substituted aromatic or heteroaromatic ring;

R^1 is =O, =NOR', halo, CN, OR', SR', SOR', SO_2R', NR'_2, NR'(CO)R', or $NR'SO_2R'$, wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), aryl (6-10C), (6-10C)aryl-(1-6C)alkyl, and (5-12C)heteroaryl- (1-6C)alkyl;

or R^1 may be an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C), (C5-C12)heteroaryl-(C1-C6)alkyl, and (C6-C12)aryl-(C1-C6)alkyl;

each R^2 is independently H, or an optionally substituted group selected from alkyl (1-8C), alkenyl (2-8C), alkynyl (2-8C), heteroalkyl (2-8C), heteroalkenyl (2-8C), heteroalkynyl (2-8C), aryl (6-10C), heteroaryl (5-12C), (5-12C)heteroaryl-(C1-C8)alkyl, and (C6-C12)aryl-(C1-C8)alkyl; and wherein both R^2 may together form an optionally substituted heterocyclic or heteroaromatic ring;

n is 0-4; and

wherein the optional substituents on each Ar, X^1, X^2 and R^2 are independently selected from halo, CN, NO_2, CF_3, OCF_3, COOR', $CONR'_2$, OR', SR', SOR', SO_2R', NR'_2, NR'(CO)R', and $NR'SO_2R'$, wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), aryl (6-10C), (6-10C)aryl-(1-6C)alkyl, and (5-12C)heteroaryl-(1-6C)alkyl;

or the optional substituents may be one or more optionally substituted groups selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C), (C6-C12)aryl-(C1-C6)alkyl and benzhydryl; and wherein two R' on a single N can cyclize to form a 3-8 membered ring containing up to two heteroatoms selected from N, O and S as ring members;

and wherein the optional substituent on X^1 and X^2 may further be selected from =O and =NOR'.

2. The method of claim 1 wherein said condition is modulated by N-type calcium channel activity.

3. The method of claim 1 wherein said condition is chronic or acute pain, a mood disorder, a neurodegenerative disorder, a gastrointestinal disorder, a genitorurinary disorder, neuroprotection, a metabolic disorder, cardiovascular disease, epilepsy, diabetes, prostate cancer, a sleep disorder, Parkinson's disease, schizophrenia or male birth control.

4. The method of any of claims 1-3, wherein X^1 is an optionally substituted alkylene(1-2C).

5. The method of claim 4 wherein X^1 is CH_2 or CO.

6. The method of any of claims 1-5, wherein X^2 is an optionally substituted alkylene(1-2C).

7. The method of claim 6 wherein X^2 is CH_2 or CO.

8. The method of any of claims 1-7, wherein each Ar is independently an optionally substituted phenyl ring.

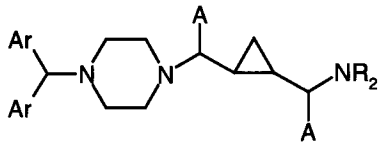
9. The method of claim 8 wherein both Ar are unsubstituted phenyl.

10. The method of any of claims 1-9, wherein n is 0-1.

11. The method of claim 10, wherein n is 0.

12. The method of any of claims 1-11, wherein at least one R^2 is other than H.

13. The method of any of claims 1-3, wherein the compound is a compound of formula (2):



(2)

or a pharmaceutically acceptable salt or conjugate thereof, wherein each A is independently H, or =O;

each Ar is independently an optionally substituted phenyl ring; and

each R is independently H, or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), C5-C12-heteroaryl-C1-C6-alkyl, and C6-C12-aryl-C1-C6-alkyl; and wherein both R may together form an optionally substituted heterocyclic or heteroaromatic ring.

14. The method of any of claims 1-3, wherein the compound is:

cyclopropane-1,2-diylbis((4-benzhydrylpiperazin-1-yl)methanone);

(4-benzhydrylpiperazin-1-yl)(2-(4-phenylpiperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-methylpiperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-morpholinopiperadine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-chlorophenyl)piperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-phenylcyclopropanecarboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyethyl)piperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-fluorophenyl)piperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyphenyl)piperazine-1-carbonyl) cyclopropyl)methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(1-phenylethyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl)cyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(3,5-dimethylpiperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropylcyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-tert-butylpiperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(methylamino)piperadine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(2,6-dimethyl-4-((4-methylcyclohexyl)methyl) piperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-((4-methylcyclohexyl)methyl)piperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-fluorophenyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-dimethylcyclopropanecarboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(morpholine-4-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(piperidine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)((1S,2S)-2-(3,5-dimethylpiperazine-1-carbonyl) cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)((1S,2S)-2-(4-*tert*-butyl-3,5-dimethylpiperazine-1-carbonyl)cyclopropyl)methanone;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropylcyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2,4,4-trimethylpentan-2-yl) cyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(heptan-4-yl) cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(pyridine-2-yl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(adamantyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(prop-2-ynyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2-methoxyethyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2-(dimethylamino)ethyl) cyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-fluorophenyl)cyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)((1S,2S)-2 –(morpholine-4-carbonyl)cyclopropyl) methanone;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2,2,6,6-tetramethyl piperidin-4-yl)cyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(cyclohexylmethyl)cyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-*tert*-butylpiperazin-1-yl)methyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-((2,44-trimethylpentan-2ylamino)methyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-((4-*tert*-butylcyclohexylamino)methyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-((*tert*-butylamino)methyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-((diisopropylamino)methyl)cyclopropyl)methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(4-methylpiperidin-1-yl)methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(3-methylpiperidin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(4-tert-butylpiperazin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(3,5-dimethylpiperazin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(morpholino)methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl) cyclopropyl)(4-methylpiperidin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl) cyclopropyl)(4-*tert*-butylpiperidin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)-N-((1-benzhydrylpyrrolidin-3-yl)methyl) cyclopropanecarboxamide;

or a pharmaceutically acceptable salt of one of these.

15. The method of any of claims 1-3, wherein the compound is:

cyclopropane-1,2-diylbis((4-benzhydrylpiperazin-1-yl)methanone);

(4-benzhydrylpiperazin-1-yl)(2-(4-phenylpiperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-fluorophenyl)piperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyphenyl)piperazine-1-carbonyl) cyclopropyl)methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(1-phenylethyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl)cyclopropane carboxamide;

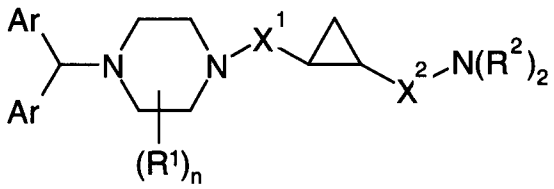
(4-benzhydrylpiperazin-1-yl)(2-(3,5-dimethylpiperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropylcyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-((4-methylcyclohexyl)methyl)piperazine-1-carbonyl)cyclopropyl) methanone;

or a pharmaceutically acceptable salt of one of these.

16. A compound of the formula:



(1)

or a pharmaceutically acceptable salt or conjugate thereof, wherein

each X^1 and X^2 is independently an optionally substituted alkylene (1-4C), alkenylene (2-4C), alkynylene (2-4C), heteroalkylene (2-4C), heteroalkenylene (2-4C), or heteroalkynylene (2-4C);

each Ar is independently an optionally substituted aromatic or heteroaromatic ring;

R^1 is =O, =NOR', halo, CN, OR', SR', SOR', SO_2R', NR'_2, NR'(CO)R', or $NR'SO_2R'$, wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), aryl (6-10C), (6-10C)aryl-(1-6C)alkyl, and (5-12C)heteroaryl- (1-6C)alkyl;

or R^1 may be an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C), (C5-C12)heteroaryl-(C1-C6)alkyl, and (C6-C12)aryl-(C1-C6)alkyl;

each R^2 is independently H, or an optionally substituted group selected from alkyl (1-8C), alkenyl (2-8C), alkynyl (2-8C), heteroalkyl (2-8C), heteroalkenyl (2-8C), heteroalkynyl (2-8C), aryl (6-10C), heteroaryl (5-12C), (5-12C)heteroaryl-(C1-C8)alkyl, and (C6-C12)aryl-(C1-C8)alkyl; and wherein both R^2 may together form an optionally substituted heterocyclic or heteroaromatic ring;

n is 0-4; and

wherein the optional substituents on each Ar, X^1, X^2 and R^2 are independently selected from halo, CN, NO_2, CF_3, OCF_3, COOR', CONR'$_2$, OR', SR', SOR', SO_2R', NR'$_2$, NR'(CO)R', and NR'SO_2R', wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C) heteroalkenyl (2-6), heteroalkynyl (2-6C), heteroaryl (5-12C), aryl (6-10C), (6-10C)aryl-(1-6C)alkyl, and (5-12C)heteroaryl-(1-6C)alkyl;

or the optional substituents may be one or more optionally substituted groups selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), O-aryl (6-10C), O-heteroaryl (5-12C), (C6-C12)aryl-(C1-C6)alkyl and benzhydryl; and wherein two R' on a single N can cyclize to form a 3-8 membered ring containing up to two heteroatoms selected from N, O and S as ring members;

and wherein the optional substituent on X^1 and X^2 may further be selected from =O and =NOR'.

17. The compound of claim 16 wherein X^1 is an optionally substituted alkylene(1-2C).

18. The compound of claim 16 wherein X^1 is CH_2 or CO.

19. The compound of any of claims 16-18, wherein X^2 is an optionally substituted alkylene(1-2C).

20. The compound of claim 19, wherein X^2 is CH_2 or CO.

21. The compound of any of claims 16-20, wherein each Ar is independently an optionally substituted phenyl ring.

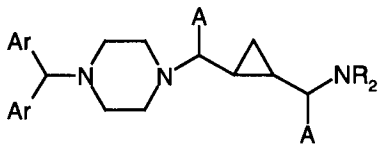
22. The compound of claim 21, wherein both Ar are unsubstituted phenyl.

23. The compound of any of claims 16-22, wherein n is 0-1.

24. The compound of claim 24 wherein n is 0.

25. The compound of any of claims 16-24, wherein at least one R^2 is other than H.

26. The compound of claim 16, which is a compound of formula (2):



(2)

or a pharmaceutically acceptable salt or conjugate thereof, wherein each A is independently H, or =O;

each Ar is independently an optionally substituted phenyl ring; and

each R is independently H, or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), heteroalkynyl (2-6C), aryl (6-10C), heteroaryl (5-12C), C5-C12-heteroaryl-C1-C6-alkyl, and C6-C12-aryl-C1-C6-alkyl; and wherein both R may together form an optionally substituted heterocyclic or heteroaromatic ring.

27. The compound of claim 16 wherein the compound is:

cyclopropane-1,2-diylbis((4-benzhydrylpiperazin-1-yl)methanone);

(4-benzhydrylpiperazin-1-yl)(2-(4-phenylpiperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-methylpiperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-morpholinopiperadine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-chlorophenyl)piperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-phenylcyclopropanecarboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyethyl)piperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-fluorophenyl)piperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyphenyl)piperazine-1-carbonyl) cyclopropyl)methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(1-phenylethyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl)cyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(3,5-dimethylpiperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropylcyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-tert-butylpiperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(methylamino)piperadine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(2,6-dimethyl-4-((4-methylcyclohexyl)methyl) piperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-((4-methylcyclohexyl)methyl)piperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-fluorophenyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-dimethylcyclopropanecarboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(morpholine-4-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(piperidine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)((1S,2S)-2-(3,5-dimethylpiperazine-1-carbonyl) cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)((1S,2S)-2-(4-*tert*-butyl-3,5-dimethylpiperazine-1-carbonyl)cyclopropyl)methanone;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-*tert*-butylcyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropylcyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2,4,4-trimethylpentan-2-yl) cyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(heptan-4-yl) cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(pyridine-2-yl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(adamantyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(prop-2-ynyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2-methoxyethyl)cyclopropane carboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2-(dimethylamino)ethyl) cyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-fluorophenyl)cyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)((1S,2S)-2 –(morpholine-4-carbonyl)cyclopropyl) methanone;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(2,2,6,6-tetramethyl piperidin-4-yl)cyclopropanecarboxamide;

(1S,2S)-2-(4-benzhydrylpiperazine-1-carbonyl)-N-(cyclohexylmethyl)cyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-*tert*-butylpiperazin-1-yl)methyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-((2,44-trimethylpentan-2ylamino)methyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-((4-*tert*-butylcyclohexylamino)methyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-((*tert*-butylamino)methyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-((diisopropylamino)methyl)cyclopropyl)methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(4-methylpiperidin-1-yl)methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(3-methylpiperidin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(4-tert-butylpiperazin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(3,5-dimethylpiperazin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)cyclopropyl)(morpholino)methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl) cyclopropyl)(4-methylpiperidin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl) cyclopropyl)(4-*tert*-butylpiperidin-1-yl) methanone;

(2-((4-benzhydrylpiperazin-1-yl)methyl)-N-((1-benzhydrylpyrrolidin-3-yl)methyl) cyclopropanecarboxamide;

or a pharmaceutically acceptable salt of one of these.

28. The compound of claim 16 wherein the compound is:

cyclopropane-1,2-diylbis((4-benzhydrylpiperazin-1-yl)methanone);

(4-benzhydrylpiperazin-1-yl)(2-(4-phenylpiperazine-1-carbonyl)cyclopropyl)methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-fluorophenyl)piperazine-1-carbonyl)cyclopropyl) methanone;

(4-benzhydrylpiperazin-1-yl)(2-(4-(2-methoxyphenyl)piperazine-1-carbonyl) cyclopropyl)methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(1-phenylethyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-*tert*-butylcyclohexyl)cyclopropane carboxamide;

2-(4-benzhydrylpiperazine-1-carbonyl)-N-(4-methylcyclohexyl)cyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(3,5-dimethylpiperazine-1-carbonyl)cyclopropyl) methanone;

2-(4-benzhydrylpiperazine-1-carbonyl)-N, N-diisopropylcyclopropane carboxamide;

(4-benzhydrylpiperazin-1-yl)(2-(4-((4-methylcyclohexyl)methyl)piperazine-1-carbonyl)cyclopropyl) methanone;

or a pharmaceutically acceptable salt of one of these.

29. A pharmaceutical composition which comprises the compound of any of claims 16-28, in admixture with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/001827

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 295/182*** (2006.01) , ***A61K 31/495*** (2006.01) , ***A61K 31/496*** (2006.01) , ***A61K 31/5377*** (2006.01) , ***C07D 401/08*** (2006.01) , ***C07D 403/08*** (2006.01) (more IPCs on the last page)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2006.01): ***C07D 295/182***, ***C07D 401/08***, ***C07D 403/08***, ***C07D 403/12***, ***C07D 413/08***, ***C07D 413/14***

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STN, Delphion (all databases), Canadian Patents Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/066446 A1 (HENDRIX, J. A. et al.) 29 August 2002 (29-08-2002) *see the claims and compound MSL827202*	1-13, 16-26 and 29
A	WO 2006/071035 A1 (LEE J. et al.) 6 July 2006 (06-07-2006) *see claim 1 and 11, compound 33*	1-29
A	WO 00/01375 A2 (SNUTCH T. P. et al.) 13 January 2000 (13-01-2000) *cited in the application*	1-29

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2007 (23-11-2007)	18 January 2008 (18-01-2008)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Guillaume Tessier 819- 934-0420

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/001827

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 1-15

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 1-15 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 1-15.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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