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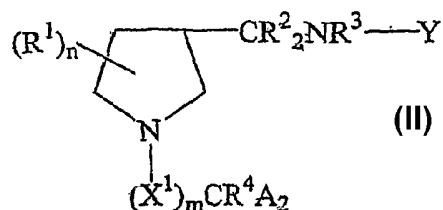
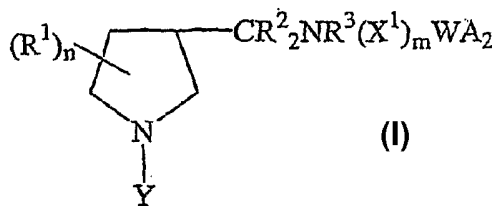
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(54) Title: 3-AMINOMETHYL-PYRROLIDINES AS N-TYPE CALCIUM CHANNEL BLOCKERS



(57) Abstract: The invention relates to compounds that are derivatives of 3-aminomethyl-pyrrolidine of the formulas: wherein: Y is (X²)₁A or (X¹)_mCR⁴A₂; W is CR⁴ or N; R¹-R⁴ are noninterfering substituents; n is 0-7; 1 and m are independently 0 or 1; X¹-X² are linkers; each A is independently a 5-7 membered optionally substituted aromatic or aliphatic ring optionally containing one or more heteroatoms selected from O, N and S. They generally contain at least one benzhydryl moiety and are useful in treating conditions which benefit from blocking calcium ion channels.

3-AMINOMETHYL-PYRROLIDINES AS N-TYPE CALCIUM CHANNEL BLOCKERS

Cross Reference to Related Applications

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. provisional application Serial No. 60/474,864 filed 30 May 2003, which is incorporated herein by reference.

Technical Field

[0002] The invention relates to compounds useful in treating conditions associated with calcium channel function. More specifically, the invention concerns compounds containing substituted or unsubstituted derivatives of 3-aminomethyl pyrrolidine-based compounds that are useful in treatment of conditions such as stroke and pain.

Background Art

[0003] Native calcium channels have been classified by their electrophysiological and pharmacological properties as T, L, N, P and Q types (for reviews see McCleskey, E. W., *et al.*, *Curr. Topics. Membr.* (1991) 39:295-326, and Dunlap, K., *et al.*, *Trends Neurosci* (1995) 18:89-98). T-type (or low voltage-activated) channels describe a broad class of molecules that transiently activate at negative potentials and are highly sensitive to changes in resting potential. The L, N, P and Q-type channels activate at more positive potentials (high voltage activated) and display diverse kinetics and voltage-dependent properties. There is some overlap in biophysical properties of the high voltage-activated channels, consequently pharmacological profiles are useful to further distinguish them. L-type channels are sensitive to dihydropyridine agonists and antagonists, N-type channels are blocked by the Conus geographus peptide toxin, ω -conotoxin GVIA, and P-type channels are blocked by the peptide ω -agatoxin IVA from the venom of the funnel web spider, *Agelenopsis aperta*. A fourth type of high voltage-activated calcium channel (Q-type) has been described, although whether the Q- and P-type channels are distinct molecular entities is controversial (Sather, W. A., *et al.*, *Neuron* (1995) 11:291-303; Stea, A., *et al.*, *Proc. Natl. Acad. Sci. USA* (1994) 91:10576-10580; Bourinet, E., *et al.*, *Nature Neuroscience* (1999) 2:407-415). Several types of calcium conductances do not fall neatly into any of the above categories and there is variability of properties even within a category suggesting that additional calcium channels subtypes remain to be classified.

[0004] Biochemical analyses show that neuronal high voltage activated calcium channels are heterooligomeric complexes consisting of at least three distinct subunits (α_1 , $\alpha_2\delta$ and β) (reviewed by De Waard, M., *et al.*, Ion Channels (1997) vol. 4, Narahashi, T., ed., Plenum Press, NY). The α_1 subunit is the major pore-forming subunit and contains the voltage sensor and binding sites for calcium channel antagonists. The mainly extracellular α_2 is disulfide-linked to the transmembrane δ subunit and both are derived from the same gene and are proteolytically cleaved *in vivo*. The β subunit is a nonglycosylated, hydrophilic protein with a high affinity of binding to a cytoplasmic region of the α_1 subunit. A fourth subunit, γ , is unique to L-type calcium channels expressed in skeletal muscle T-tubules. The isolation and characterization of γ -subunit-encoding cDNA's is described in U.S. Pat. No. 5,386,025 which is incorporated herein by reference.

[0005] Recently, each of these α_1 subtypes has been cloned and expressed, thus permitting more extensive pharmacological studies. These channels have been designated α_{1A} , α_{1I} and α_{1S} and correlated with the subtypes set forth above. α_{1A} channels are of the P/Q type; α_{1B} represents N-type; α_{1C} , α_{1D} , α_{1F} and α_{1S} represent L-type; α_{1E} represents a novel type of calcium conductance, and α_{1G} - α_{1I} represent members of the T-type family, reviewed in Stea, A., *et al.*, in Handbook of Receptors and Channels (1994), North, R. A. ed. CRC Press; Perez-Reyes, *et al.*, *Nature* (1998) 391:896-900; Cribbs, L. L., *et al.*, *Circulation Research* (1998) 83:103-109; Lee, J. H., *et al.*, *Journal of Neuroscience* (1999) 19:1912-1921.

[0006] Further details concerning the function of N-type channels, which are mainly localized to neurons, have been disclosed, for example, in U.S. Pat. No. 5,623,051, the disclosure of which is incorporated herein by reference. As described, N-type channels possess a site for binding syntaxin, a protein anchored in the presynaptic membrane. Blocking this interaction also blocks the presynaptic response to calcium influx. Thus, compounds that block the interaction between syntaxin and this binding site would be useful in neural protection and analgesia. Such compounds have the added advantage of enhanced specificity for presynaptic calcium channel effects.

[0007] 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; among the substituents permitted are piperazine derivatives, including their benzhydryl derivatives. U.S. Pat. No. 5,428,038 discloses compounds which are said to exert a neural protective and antiallergic effect. These compounds are coumarin derivatives which may include derivatives of piperazine and other six-membered heterocycles. A permitted substituent on the heterocycle is diphenylhydroxymethyl. Thus, approaches in the art for various indications which may involve calcium channel blocking activity have employed compounds which incidentally contain piperidine or piperazine moieties substituted with benzhydryl but mandate additional substituents to maintain functionality.

[0008] 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; Lomerizine is, however, 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.

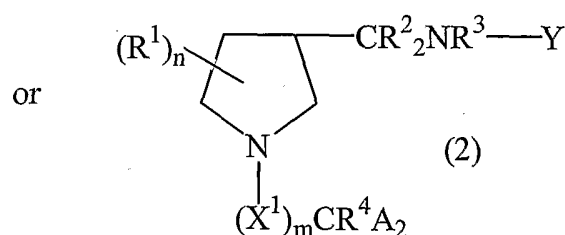
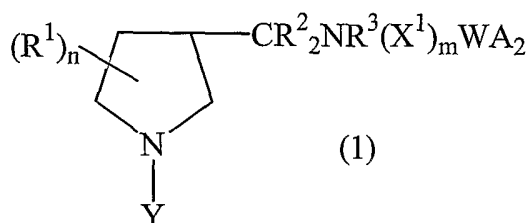
[0009] U.S. Pat. Nos. 6,011,035; 6,294,533; 6,310,059; and 6,387,897 describe selective N-type calcium channel blockers that were designed based on the recognition that the combination of a piperazine or piperidine ring coupled through a linker to a benzhydryl moiety results in effective calcium channel blocking activity. The present invention is based on the observation that substitution of the piperazine or piperidine ring with 3-aminomethyl pyrrolidine results in unexpectedly high affinity for N-type calcium channels.

[0010] The compounds are useful for treating stroke, pain, anxiety and other calcium channel-associated disorders, as further described below. By focusing on these moieties, compounds useful in treating indications associated with calcium channel activity are prepared.

Disclosure of the Invention

[0011] The invention relates to compounds useful in treating conditions such as stroke, anxiety, overactive bladder, inflammatory bowel disease, head trauma, migraine, chronic, neuropathic and acute pain, epilepsy, hypertension, cardiac arrhythmias, and other indications

associated with calcium metabolism, including synaptic calcium channel-mediated functions. The compounds of the invention are benzhydryl or partly saturated benzhydryl derivatives of 3-substituted pyrrolidine with substituents which enhance the calcium channel blocking activity of the compounds. Thus, in one aspect, the invention is directed to compounds of formulas (1) and (2) and therapeutic methods that employ these compounds. The compounds of the invention are those of the formulas:



wherein:

Y is $(X^2)_lA$ or $(X^1)_mCR^4A_2$;

W is CR^4 or N;

R^1 - R^4 are noninterfering substituents;

n is 0-7;

l and m are independently 0 or 1;

X^1 - X^2 are linkers;

each A is independently a 5-7 membered optionally substituted aromatic or aliphatic ring optionally containing one or more heteroatoms selected from O, N and S.

[0012] The compounds of the invention may be in the form of a salt if appropriate or in the form of a prodrug. With respect to compounds of the invention that contain chiral centers (and each compound of the invention contains at least one chiral center) the compounds may be in the form of isolated stereoisomers or mixtures of various stereoisomers, including enantiomeric mixtures, equimolar mixtures of all possible stereoisomers, or various degrees of chiral or optical purity.

[0013] The linkers represented by X^1 - X^2 are alkylene or alkenylene moieties optionally including one or more hetero-atoms selected from N, O, and S and optionally containing the non interfering substitutions. The number of members in the chain in the linkers is 1-10.

[0014] Noninterfering substituents generally are independently optionally substituted alkyl (1-10C), alkenyl (2-10C), alkynyl (2-10C), aryl (5-12 ring members), arylalkyl (7-16C) or arylalkenyl (7-16C) each optionally having one or more C, generally 1-4C, replaced by heteroatoms (N, O and/or S) and wherein said optional substituents on alkyl, alkenyl, etc., may

include one or more =O. Thus substituents include embodiments wherein these substituents may form an acyl, amide, or ester linkage with the atom to which it is bound. The substituents include, as well, one or more halo, CF₃, CN, OCF, NO₂, NO, SO, SO₂, NR₂, OR, SR, COOR, and/or CONR₂, wherein R is H or optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, or arylalkenyl, as described above, and wherein S may be oxidized, and wherein two substituents may form a 3-7 membered saturated or unsaturated ring, said ring optionally itself substituted and optionally containing one or more heteroatoms (N, S, O). When a substituent shown in a formula is mandatory, it may also be H.

[0015] Thus, in some embodiments, non-interfering substituents in general include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, =O, halo, OR, NR₂, SR, -SOR, -SO₂R, -OCOR, -NRCOR, -NRCONR₂, -NRCOOR, -OCONR₂, -RCO, -COOR, SO₂R, NRSOR, NRSO₂R, -SO₃R, -CONR₂, SO₂NR₂, wherein each R is independently H or alkyl (1-8C), CN, CF₃, and NO₂, and like substituents.

[0016] The invention is directed to methods to antagonize calcium channel activity using the compounds of formulas (1) and (2) and thus to treat associated conditions. It will be noted that the conditions may be associated with undesired calcium channel activity, or the subject may have normal calcium channel function which nevertheless results in an undesirable physical or metabolic state. In another aspect, the invention is directed to pharmaceutical compositions containing these compounds.

[0017] The invention is also directed to combinatorial libraries containing the compounds of formulas (1) and (2) and to methods to screen these libraries for members containing particularly potent calcium channel blocking activity or for members that antagonize one type of such channels specifically.

Brief Description of the Drawings

[0018] Figure 1 shows the names and structures of illustrative compounds of the invention.

[0019] Figure 2 is a graph showing the selectivity of compound P13 for N-, P/Q- and L-type channels.

[0020] Figure 3 is a graph showing the selectivity of compound P17 for N-, P/Q- and L-type channels.

Modes of Carrying Out the Invention

[0021] The compounds of formulas (1) and (2), useful in the methods of the invention, exert their desirable effects through their ability to antagonize the activity of calcium channels. This makes them useful for treatment of certain conditions. Among such conditions are chronic pain conditions such as neuropathic pain, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, AIDS related neuropathy, cancer pain, inflammatory pain, osteoarthritis pain, rheumatoid arthritis pain and fibromyalgia; acute pain; nociceptive pain; post-operative pain; mood disorders; anxiety disorders such as generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive compulsive disorder and post-traumatic stress syndrome; depression; addiction disorders such as cocaine dependence and withdrawal, opioid dependence and withdrawal, alcohol dependence and withdrawal and nicotine dependence and withdrawal; gastrointestinal disorders such as inflammatory bowel disease and irritable bowel syndrome; and genitourinary disorders such as urinary incontinence, interstitial colitis and sexual dysfunction.

[0022] T-type calcium channels have been implicated in the following conditions: cardiovascular diseases such as hypertension, arrhythmias, atrial fibrillation congestive heart failure and angina pectoris; epilepsy conditions such as partial seizures, temporal lobe epilepsy, absence seizures, generalized seizures and tonic/clonic seizures; diabetes and cancer. T-type calcium channels are also involved in chronic pain conditions such as neuropathic pain, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, AIDS related neuropathy, cancer pain, inflammatory pain, osteoarthritis pain, rheumatoid arthritis pain and fibromyalgia; acute pain; nociceptive pain and post-operative pain.

[0023] While the compounds of formulas (1) and (2) generally have this activity, the availability of a multiplicity of calcium channel blockers permits a nuanced selection of compounds for particular disorders. Thus, the availability of this class of compounds provides not only a genus of general utility in indications that are affected by calcium channel activity, but also provides a large number of compounds which can be mined and manipulated for specific interaction with particular forms of calcium channels. The availability of recombinantly produced calcium channels of the α_{1A} - α_{1I} and α_{1S} types set forth above, facilitates this selection process. Dubel, S. J., *et al.*, *Proc Natl Acad Sci USA* (1992) 89:5058-5062; Fujita, Y., *et al.*, *Neuron* (1993) 10:585-598; Mikami, A., *et al.*, *Nature* (1989) 340:230-233; Mori, Y., *et al.*, *Nature* (1991) 350:398-402; Snutch, T. P., *et al.*, *Neuron* (1991) 7:45-57; Soong, T. W., *et al.*, *Science* (1993) 260:1133-1136; Tomlinson, W. J., *et al.*,

Neuropharmacology (1993) 32:1117-1126; Williams, M. E., *et al.*, *Neuron* (1992) 8:71-84; Williams, M. E., *et al.*, *Science* (1992) 257:389-395; Perez-Reyes, *et al.*, *Nature* (1998) 391:896-900; Cribbs, L. L., *et al.*, *Circulation Research* (1998) 83:103-109; Lee, J. H., *et al.*, *Journal of Neuroscience* (1999) 19:1912-1921; McRory, J. E., *et al.*, *Journal of Biological Chemistry* (2001) 276:3999-4011.

[0024] Thus, while it is known that calcium channel activity is involved in a multiplicity of disorders, the types of channels associated with particular conditions is the subject of ongoing data collection. For example, the association of N-type channels in conditions associated with neural transmission would indicate that compounds of the invention which target N-type channels are most useful in these conditions. Many of the members of the genus of compounds of formulas (1) and (2) exhibit high affinity for N-type and/or T-type channels; other members of the genus may preferentially target other channels.

[0025] 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.

[0026] 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 inactive state.

[0027] 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.

[0028] 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 enzymes since these enzymes are required for drug detoxification. Finally, the compound will be evaluated for calcium ion channel type specificity by comparing its activity among the various types of calcium channels, and specificity for one particular channel type is preferred. The compounds which progress through these tests successfully are then examined in animal models as actual drug candidates.

The Invention Compounds

[0029] In the compounds of formulas (1) and (2), the following describes the nature of the various components.

[0030] The ring represented by A is preferably optionally substituted phenyl, cyclohexyl, 2-, 3- or 4-pyridyl, indolyl, 2- or 4-pyrimidyl, pyridazinyl, benzotriazolyl or benzimidazolyl. More preferably A is phenyl, cyclohexyl, pyridyl, or pyrimidyl. Most preferably A is cyclohexyl or phenyl. Each of these embodiments may optionally be substituted with a group defined herein such as optionally substituted alkyl, alkenyl, alkynyl, aryl, O-aryl, O-alkylaryl, O-aroyl, NR-aryl, N-alkylaryl, NR-aroyl, halo, OR, NR₂, SR, -OOCR, -NROCR, RCO, -COOR, -CONR₂, and/or SO₂NR₂, wherein each R is independently H or alkyl (1-8C), and/or by CN, CF₃, and/or NO₂, for example. Alkyl, alkenyl, alkynyl and aryl portions of these may be further substituted by similar substituents.

[0031] The rings represented by A may optionally be substituted with an inorganic substituent or an organic substituent comprising 15 non-hydrogen atoms or less. These substituents include optionally substituted alkyl (1-10C), optionally substituted alkenyl (2-10C), optionally substituted alkynyl (2-10C), an additional aryl moiety (5-12 ring members), arylalkyl, arylalkenyl or arylalkynyl (wherein aryl, alkyl, alkenyl and alkynyl are as defined above) and wherein in any of the foregoing, one or more carbons may be replaced by a heteroatom selected from O, S, and/or N. Each A may also independently and optionally be substituted by one or more inorganic moieties such as halo, nitro, sulfhydryl, hydroxyl, amino,

or forms of OH, SH, or NH₂ wherein the H is replaced with optionally substituted organic moieties selected from those listed hereinabove. These moieties may in turn be further substituted as described. These substituents, specifically, may include =O.

[0032] Among preferred substituents on A are tert-butyl, methoxy, substituted alkoxy, hydroxy and halo.

[0033] Preferred embodiments of Y include those wherein A is phenyl (Φ) or a partially saturated or fully saturated form thereof (Cy) such as CH₂ Φ , CO Φ , CH Φ ₂, CH₂CH₂X⁴ Φ , COCH₂X⁴ Φ , CH₂Cy, CH₂Cy₂ and CHCy Φ , wherein X⁴ is C = O, NR³, NCO, S, or O and where each Φ or Cy is unsubstituted or substituted with 1-3 substituents.

[0034] The 1-3 substituents are independently selected from halo, CF₃, OCF, lower alkyl (1-6C), lower aryl (6-10C) and arylalkyl (7-16C) optionally containing 1-4 heteroatoms (N, O, or S) and optionally substituted with inorganic substituents (comprising halo, N, P, O or S). Thus, these substituents may be, for example, halo, NO₂, NR₂, OR, SR, COR, COOR, CONR₂, NROCR, OOCR where R = H or alkyl (1-8C). Two substituents may form a 3-7 member ring optionally containing a heteroatom (N,S,O).

[0035] R¹ is a noninterfering substituent and n is 0-7, preferably 0-2, and most preferably 0-1. If n is 2 or 3, it is preferred that each R¹ occupy a different position on the pyrrolidine ring. Noninterfering substituents encompassed by R¹ include lower alkyl (1-6C), lower alkenyl (2-6C) and lower alkynyl (2-6C) optionally including one or more heteroatom selected from O, N and S, including substituted forms thereof comprising inorganic substituents such as halo, NO₂, SO₂, SO, NO and the like; R¹ may itself be one of these inorganic substituents. Two R¹ together on the same carbon may be =O or =NOH.

[0036] Preferred embodiments of R² include H, lower alkyl, lower alkenyl, and halo, preferably H or lower alkyl, and more preferably H. It is preferred that at least one of R² be H. Preferred embodiments of R³ include H, lower alkyl, lower alkenyl, lower acyl, and these embodiments wherein one or more carbons is replaced with a heteroatom. Especially preferred for R³ is H or CONCH₂CH₃.

[0037] Preferred embodiments for R⁴ include H, alkyl, alkenyl, arylalkyl, arylalkenyl, hydroxy, alkoxy, sulfhydryl, alkylsulfhydryl, amino, and alkylamino. Especially preferred are H, hydroxy, and alkoxy.

[0038] X¹ may be present or absent (m is 0 or 1) and is a linker which spaces the benzhydryl moiety from either the ring nitrogen or the nitrogen on the 3-aminomethyl substituent on the pyrrolidine. Typically, X¹ is an alkylene or alkenylene which is optionally

substituted, wherein one particularly favored substitution is =O at the carbon adjacent the nitrogen to which X¹ is coupled. The alkylene or alkenylene chain may contain 1-10 members, preferably 1-8 members, more preferably 1-5 members and preferably is unsubstituted or contains a single substitution of =O at the carbon adjacent N. This chain, may also have one or more carbons replaced by a heteroatom, preferably N or O; preferably only a single heteroatom replaces a single carbon.

[0039] X² is defined as X¹; in general, X² contains an additional chain member as compared to X¹.

[0040] As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight-chain, branched-chain and cyclic monovalent substituents, containing only C and H when they are unsubstituted or unless otherwise noted. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butenyl, and the like. Typically, the alkyl, alkenyl and alkynyl substituents contain 1-10C (alkyl) or 2-10C (alkenyl or alkynyl). Preferably they contain 1-6C (lower alkyl) or 2-6C (lower alkenyl or lower alkynyl).

[0041] Additional examples of optionally substituted alkyl groups include propyl, tert-butyl, etc., and including cycloalkyls such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.; examples of optionally substituted alkenyl groups include allyl, crotyl, 2-pentenyl, 3-hexenyl, 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.; C₁₋₆ alkyl and alkenyl are preferred.

[0042] Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined but may contain one or more O, S or N heteroatoms or combinations thereof within the backbone residue.

[0043] As used herein, "acyl" encompasses the definitions of alkyl, alkenyl, alkynyl, each of which is coupled to an additional residue through a carbonyl group. Heteroacyl includes the related heteroforms.

[0044] "Aromatic" moiety or "aryl" moiety refers to a monocyclic or fused bicyclic moiety such as phenyl or naphthyl; "heteroaromatic" also refers to monocyclic or fused bicyclic ring systems containing one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits inclusion of 5-membered rings as well as 6-membered rings. Thus, typical aromatic/heteroaromatic systems include pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl and the like. Because tautomers are theoretically possible, phthalimido is also considered aromatic. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring

system is included in this definition. Typically, the ring systems contain 5-12 ring member atoms.

[0045] Similarly, "arylalkyl" and "heteroarylalkyl" refer to aromatic and heteroaromatic systems which are coupled to another residue through a carbon chain, including substituted or unsubstituted, saturated or unsaturated, carbon chains, typically of 1-8C, or the hetero forms thereof. These carbon chains may also include a carbonyl group, thus making them able to provide substituents as an acyl or heteroacyl moiety.

[0046] In general, any alkyl, alkenyl, alkynyl, acyl, or aryl 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 primary substituents themselves. Thus, where an embodiment of a substituent is alkyl, this alkyl may optionally be substituted by the remaining substituents listed as substituents where this makes chemical sense, and where this does not undermine the size limit of alkyl *per se*; e.g., alkyl substituted by alkyl or by alkenyl would simply extend the upper limit of carbon atoms for these embodiments. However, alkyl substituted by aryl, amino, alkoxy, and the like would be included.

[0047] Examples of halogen include fluorine, chlorine, bromine, iodine, etc., with fluorine and chlorine preferred.

[0048] Examples of optionally substituted hydroxyl and thiol groups include optionally substituted alkyloxy or alkylthio (e.g., C₁₋₁₀ alkyl) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.); an optionally substituted arylalkyloxy or arylalkylthio (e.g., phenyl-C₁₋₄ alkyl, e.g., benzyl, phenethyl, etc.). Where there are two adjacent hydroxyl or thiol substituents, the heteroatoms may be connected via an alkylene group such as O(CH₂)_nO and S(CH₂)_nS (where n=1-5). Examples include methylenedioxy, ethylenedioxy, etc. Oxides of thio-ether groups such as sulfoxides and sulfones are also envisioned.

[0049] Examples of optionally substituted hydroxyl groups also include optionally substituted C₂₋₄alkanoyl (e.g., acetyl, propionyl, butyryl, isobutyryl, etc.), C₁₋₄ alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.) and an optionally substituted aromatic and heterocyclic carbonyl group including benzoyl, pyridinecarbonyl, etc.

[0050] Substituents on optionally substituted amino groups may bind to each other to form a cyclic amino group (e.g., 5- to 6-membered cyclic amino, etc., such as tetrahydropyrrole, piperazine, piperidine, pyrrolidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.). Said cyclic amino group may have a substituent, and examples of the substituents include halogen

(*e.g.*, fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (*e.g.*, trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (*e.g.*, methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₂₋₄ alkanoyl (*e.g.*, acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (*e.g.*, methanesulfonyl, ethanesulfonyl, etc.) the number of preferred substituents are 1 to 3.

[0051] An amino group may also be substituted once or twice (to form a secondary or tertiary amine) with a group such as an optionally substituted alkyl group including C₁₋₁₀alkyl (*e.g.*, methyl, ethyl propyl etc.); an optionally substituted alkenyl group such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., or an optionally substituted cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. In these cases, C₁₋₆ alkyl, alkenyl and cycloalkyl are preferred. The amine group may also be optionally substituted with an aromatic or heterocyclic group, aralkyl (*e.g.*, phenylC₁₋₄alkyl) or heteroalkyl for example, phenyl, pyridine, phenylmethyl (benzyl), phenethyl, pyridinylmethyl, pyridinylethyl, etc. The heterocyclic group may be a 5 or 6 membered ring containing 1-4 heteroatoms.

[0052] An amino group may be substituted with an optionally substituted C₂₋₄ alkanoyl, *e.g.*, acetyl, propionyl, butyryl, isobutyryl etc., or a C₁₋₄alkylsulfonyl (*e.g.*, methanesulfonyl, ethanesulfonyl, etc.) or a carbonyl or sulfonyl substituted aromatic or heterocyclic ring, *e.g.*, benzenesulfonyl, benzoyl, pyridinesulfonyl, pyridinecarbonyl etc. The heterocycles are as defined above.

[0053] Examples of optionally substituted carbonyl groups, or sulfonyl groups include optionally substituted forms of such groups formed from various hydrocarbyls such as alkyl, alkenyl and 5- to 6-membered monocyclic aromatic group (*e.g.*, phenyl, pyridyl, etc.), as defined above.

[0054] The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Examples of inorganic bases with alkali metal hydroxides (*e.g.*, sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxides (*e.g.*, of calcium, magnesium, etc.), and hydroxides of aluminum, ammonium, etc. Examples of organic bases include trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Examples of inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Examples of organic acids

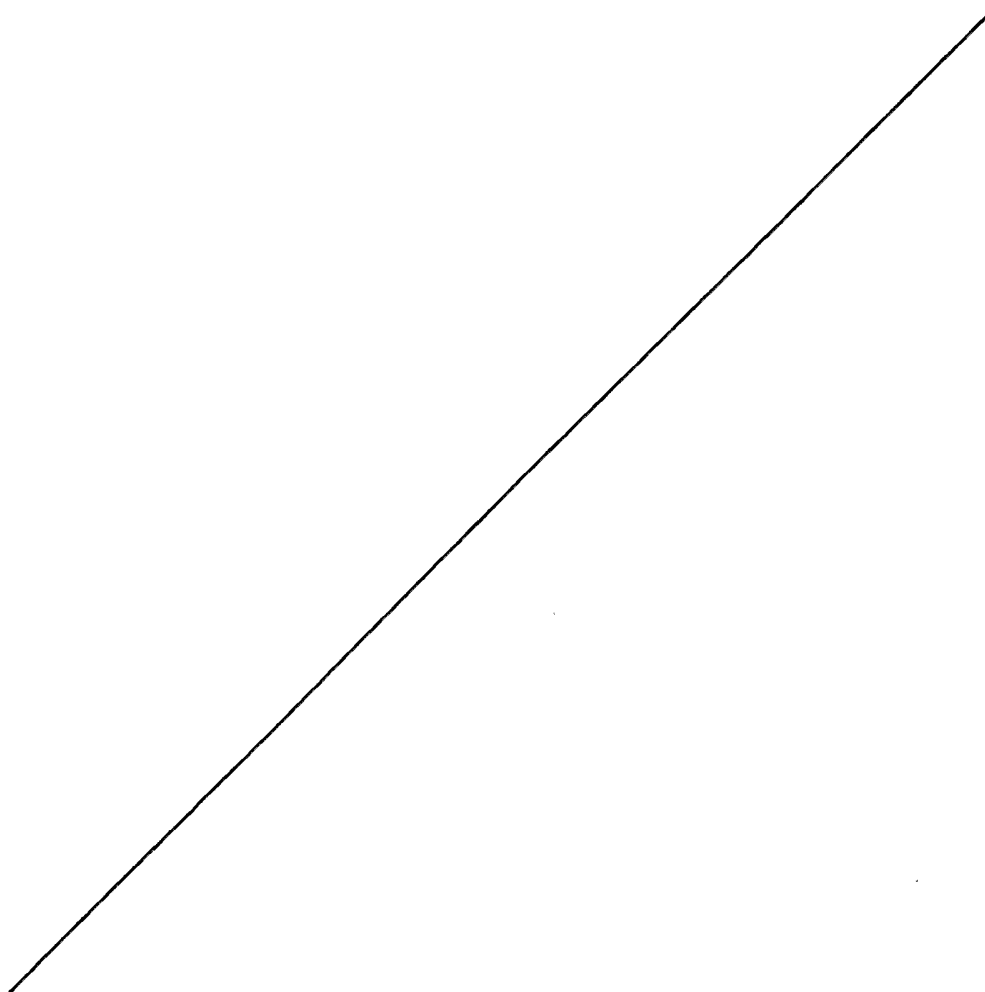
include formic acid, oxalic acid, acetic acid, tartaric acid, methanesulfonic acid, benzenesulfonic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Also included are salts with basic amino acids such as arginine, lysine, ornithine, etc., and salts with acidic amino acids such as aspartic acid, glutamic acid, etc.

[0055] In addition, in some cases, the compounds of the invention contain one or more chiral centers. The invention includes the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity.

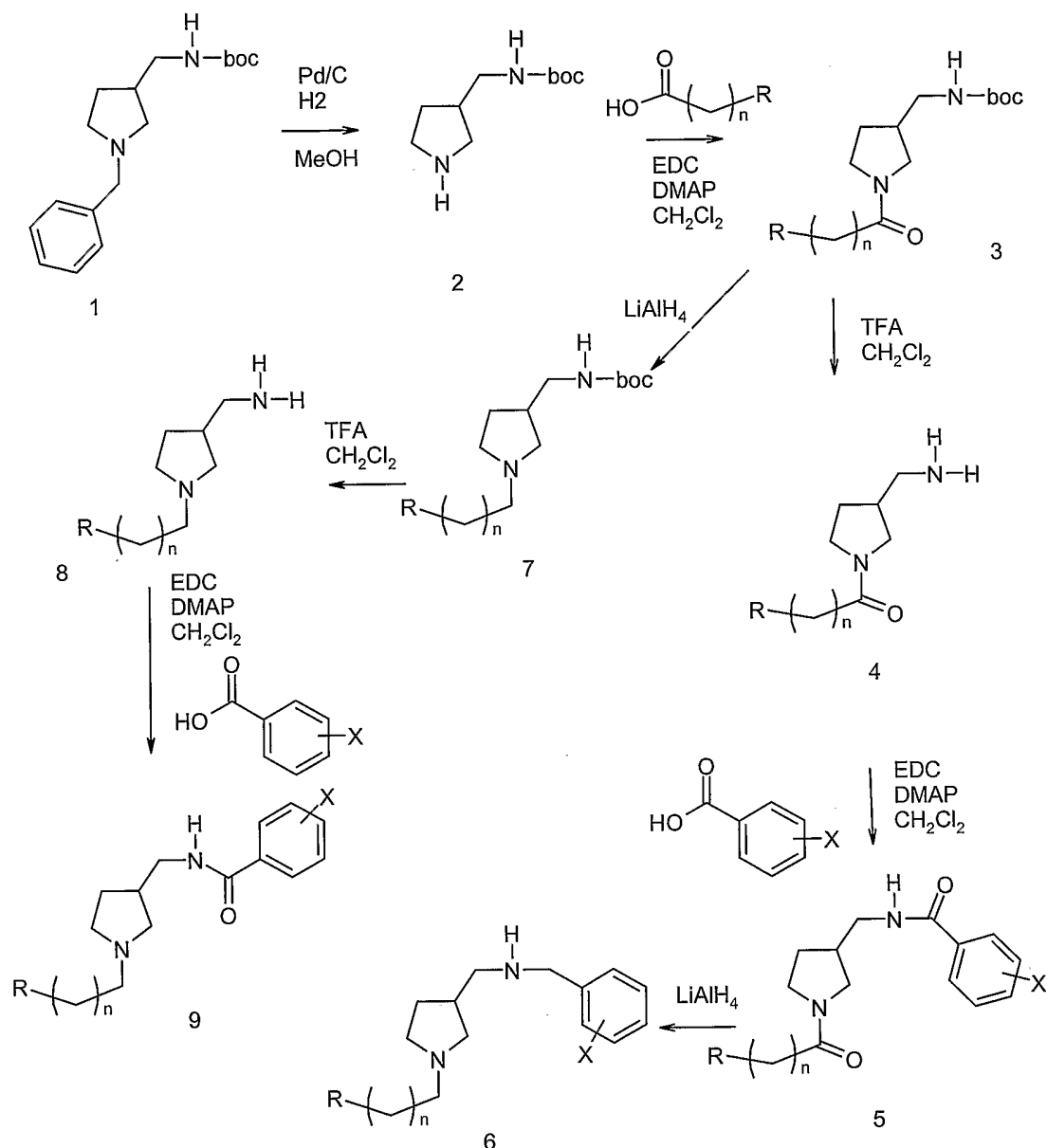
Synthesis of the Invention Compounds

[0056] The compounds of the invention may be synthesized using conventional methods. Illustrative of such methods are Schemes A, B, C, D, E, F, G and H.

[0057] Reaction Scheme A may be used to synthesize compounds of the invention such as P3, P4, P7, P8, P13, P14, P15, P17, P18, P19, P20, P21, P22, P24 and P25.



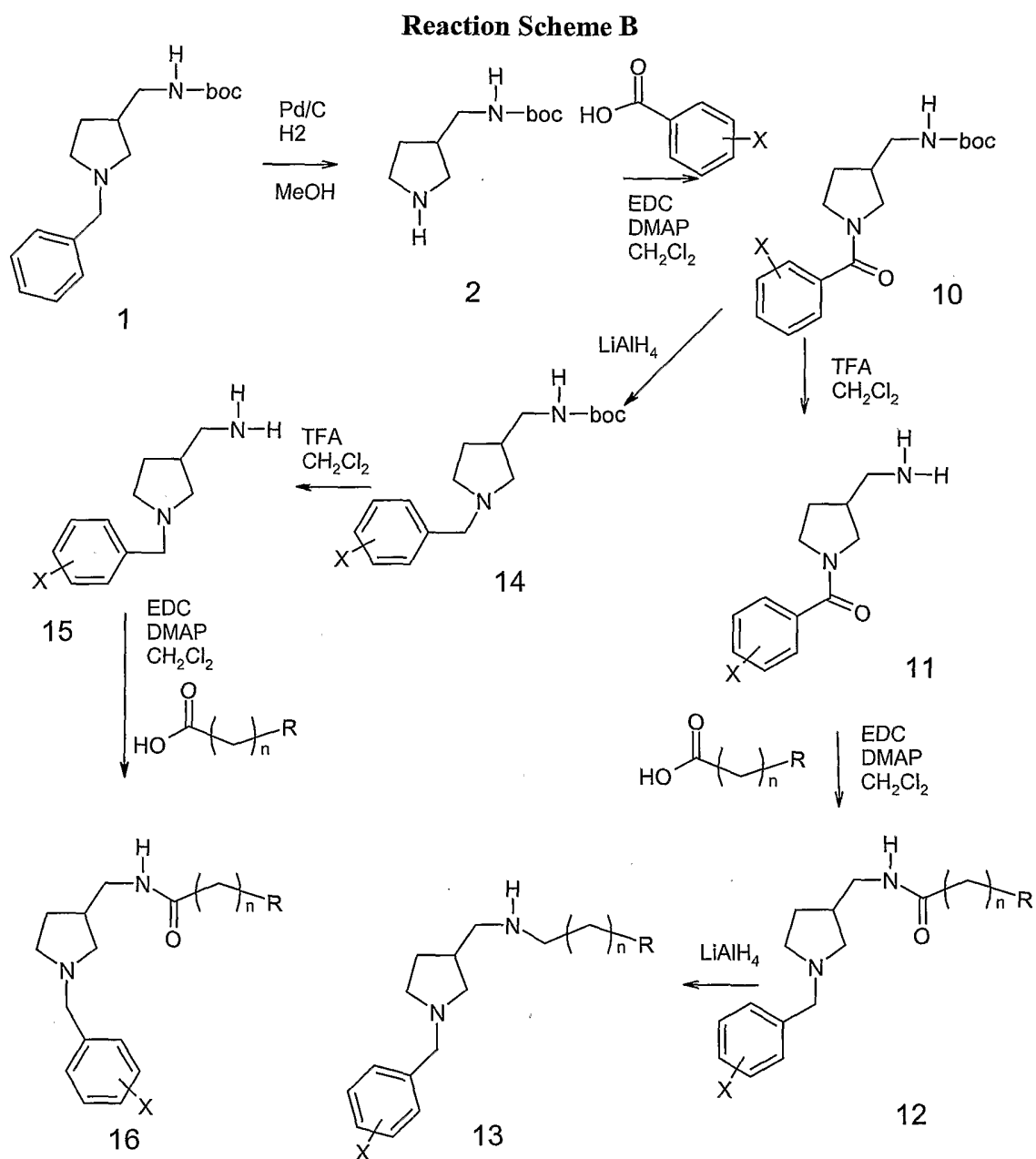
Reaction Scheme A



[0058] Treatment of commercially available (1-benzyl-pyrrolidin-3-ylmethyl)-carbamic acid tert-butyl ester (1) with Pd/C at 50 psi gives unprotected 3-aminomethyl-3-tert-butoxycarbonylpyrrolidine (2) in quantitative yield. Coupling of (2) with suitable carboxylic acid using EDC/DMAP in CH_2Cl_2 gives (3). Removal of BOC using TFA gives (4). Coupling of (4) with suitable benzoic acid derivatives under usual condition followed by reduction of amide with LiAlH_4 using aprotic solvent (THF) gives (6).

[0059] Reduction of amide (3) with LiAlH_4 followed by removal of BOC gives (8). Coupling of (8) with suitable benzoic acid derivatives gives (9).

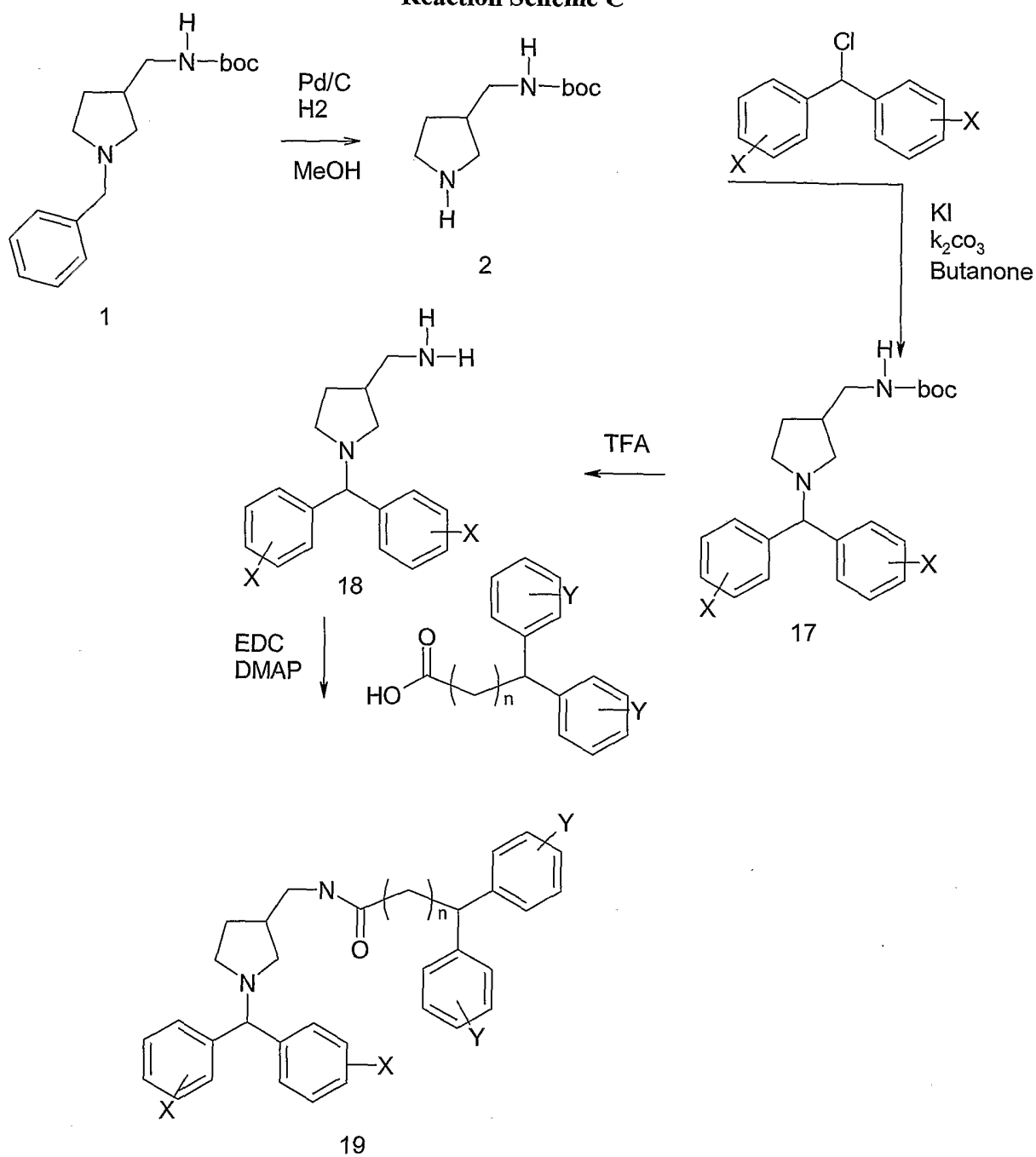
[0060] Reaction Scheme B may be used to synthesize compounds of the invention such as P5, P6, P9, P10, P11, P12 and P23.



[0061] Treatment of (2) with suitable benzoic acid derivatives under usual condition (EDC/DMAP , CH_2Cl_2) followed by removal of BOC and coupling with suitable carboxylic acid and reduction of amide gives (13) in a good yield. Subsequently (10) was reduced followed by removal of BOC and coupling with carboxylic acid gives (16).

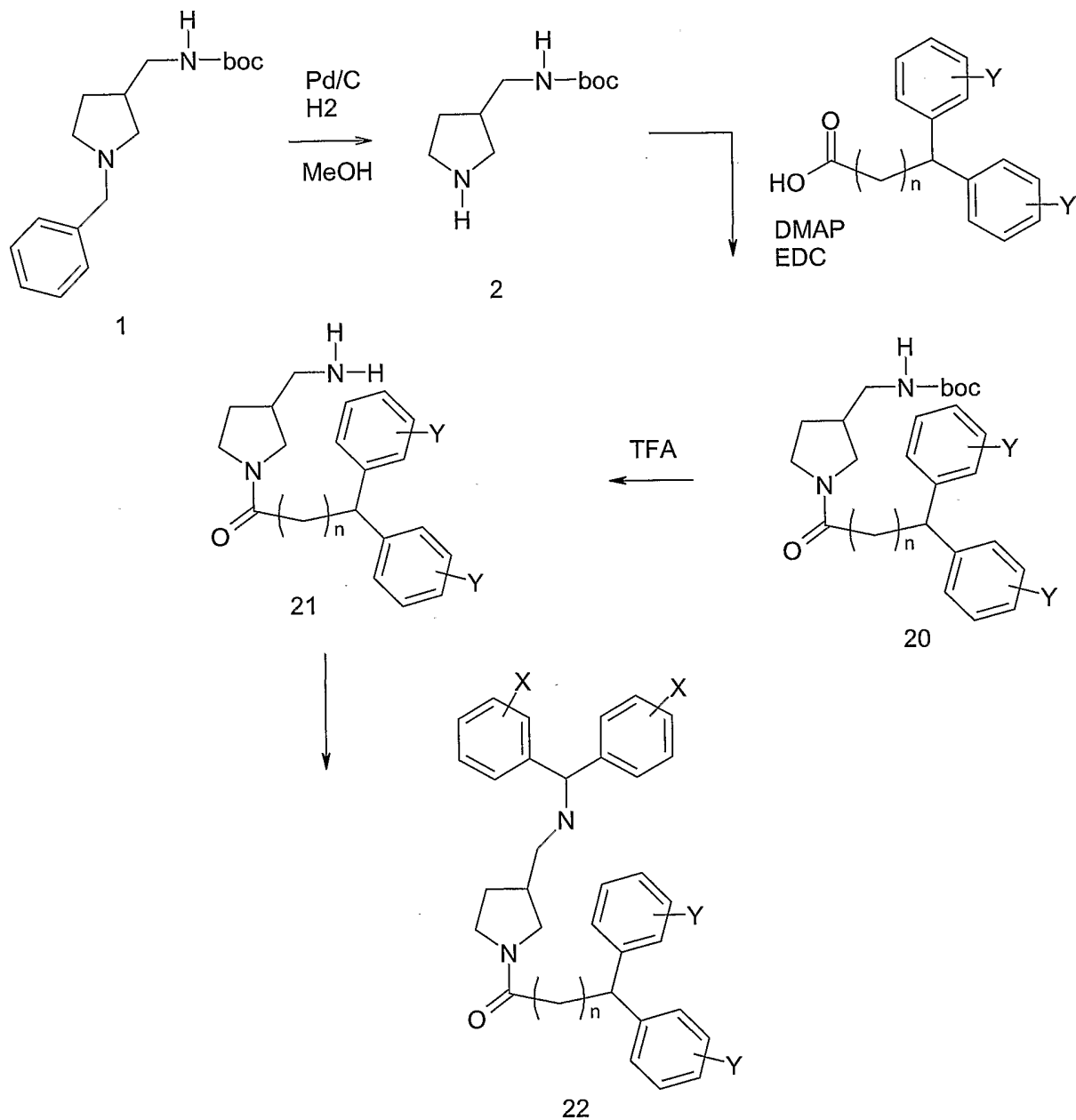
[0062] Reaction Scheme C may be used to synthesize compounds of the invention such as P1, P32, P37, P38 and P39.

Reaction Scheme C



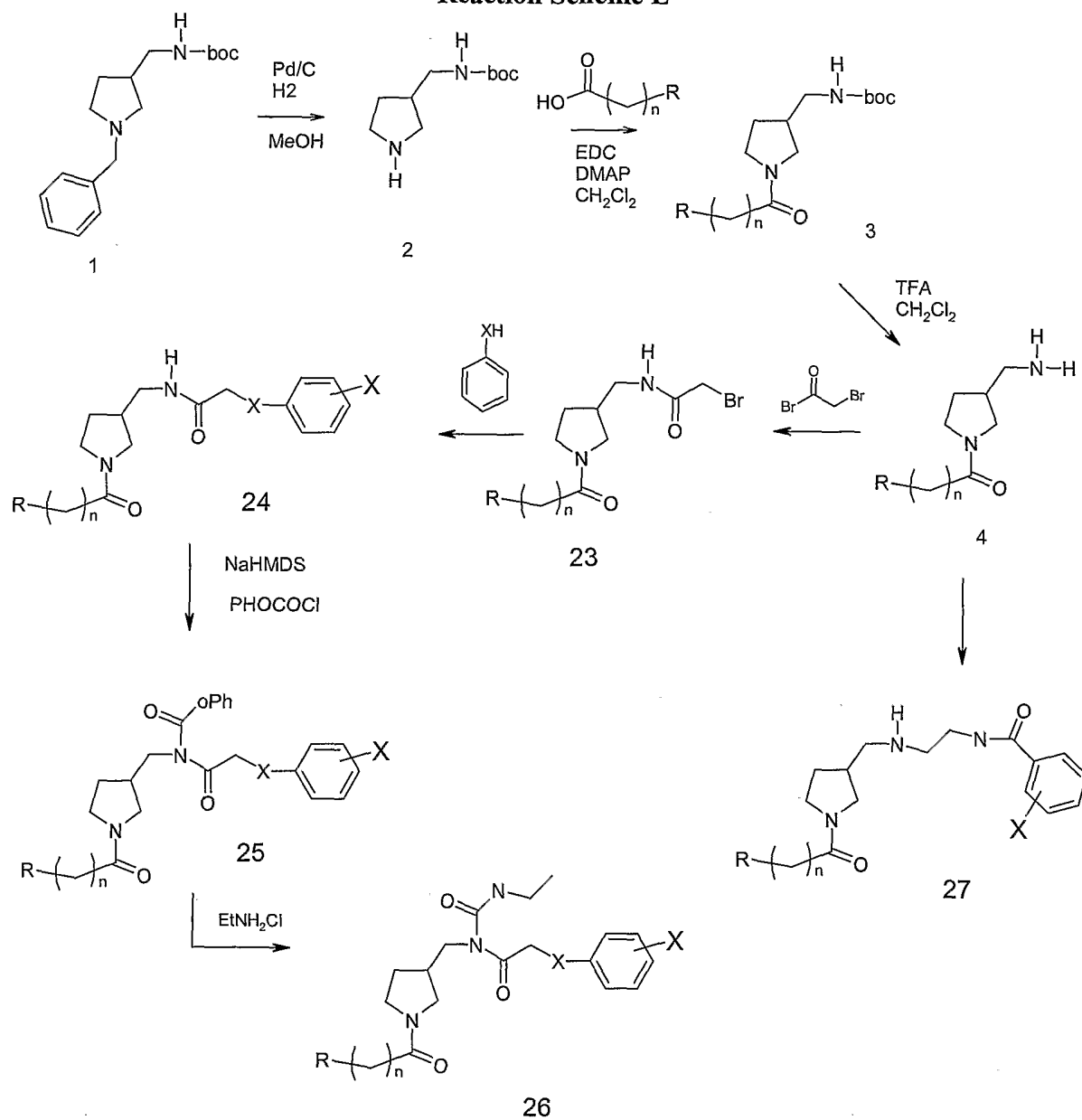
[0063] Treatment of (2) with chlorodiphenylmethane using $\text{KI}/\text{K}_2\text{CO}_3/\text{Butanone}$ reflux overnight gives (17). Reaction of (17) with TFA followed by coupling with suitable carboxylic acid gives (19).

[0064] Reaction Scheme D may be used to synthesize compounds of the invention such as P2.

Reaction Scheme D

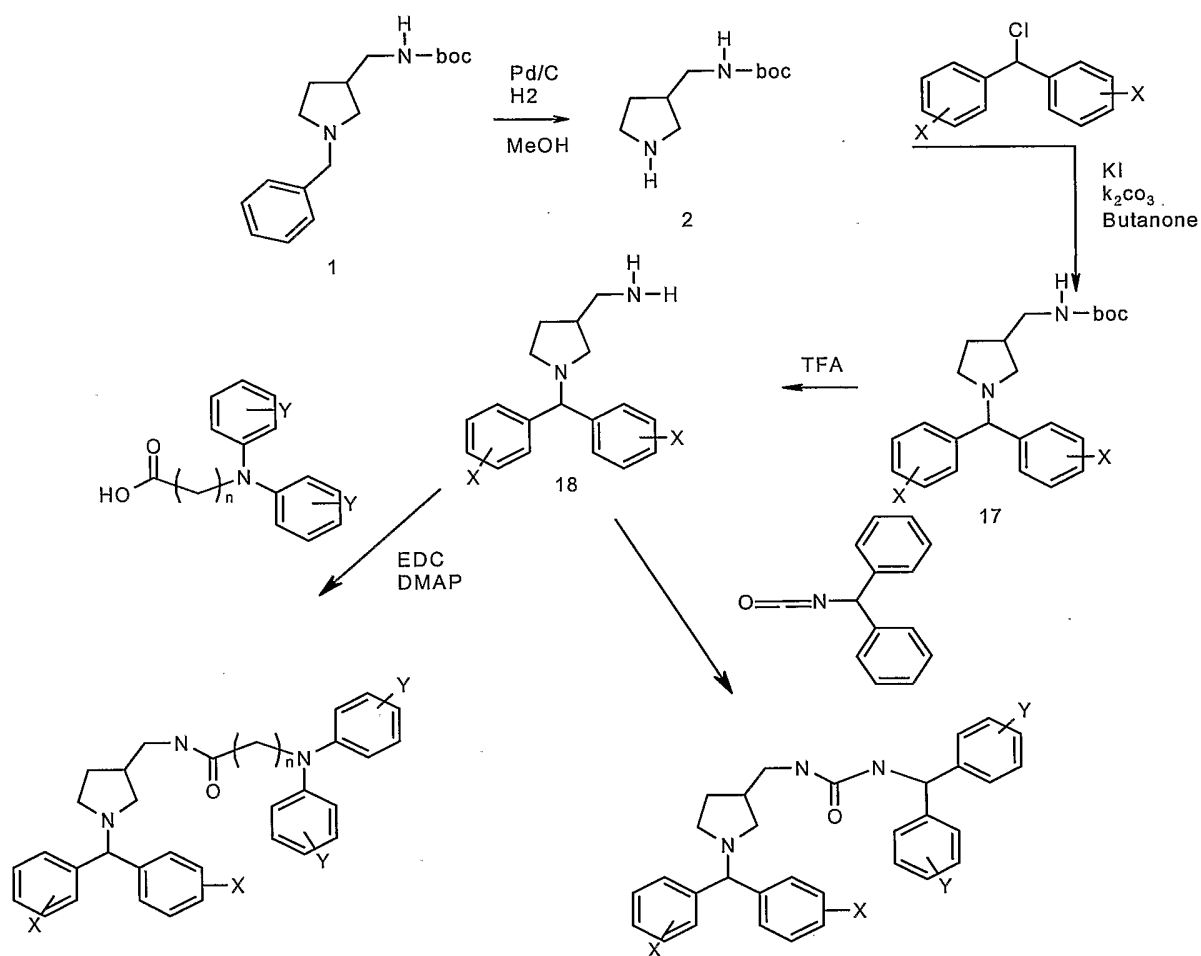
[0065] Compounds of the invention may also be synthesized using Reaction Scheme E.

Reaction Scheme E

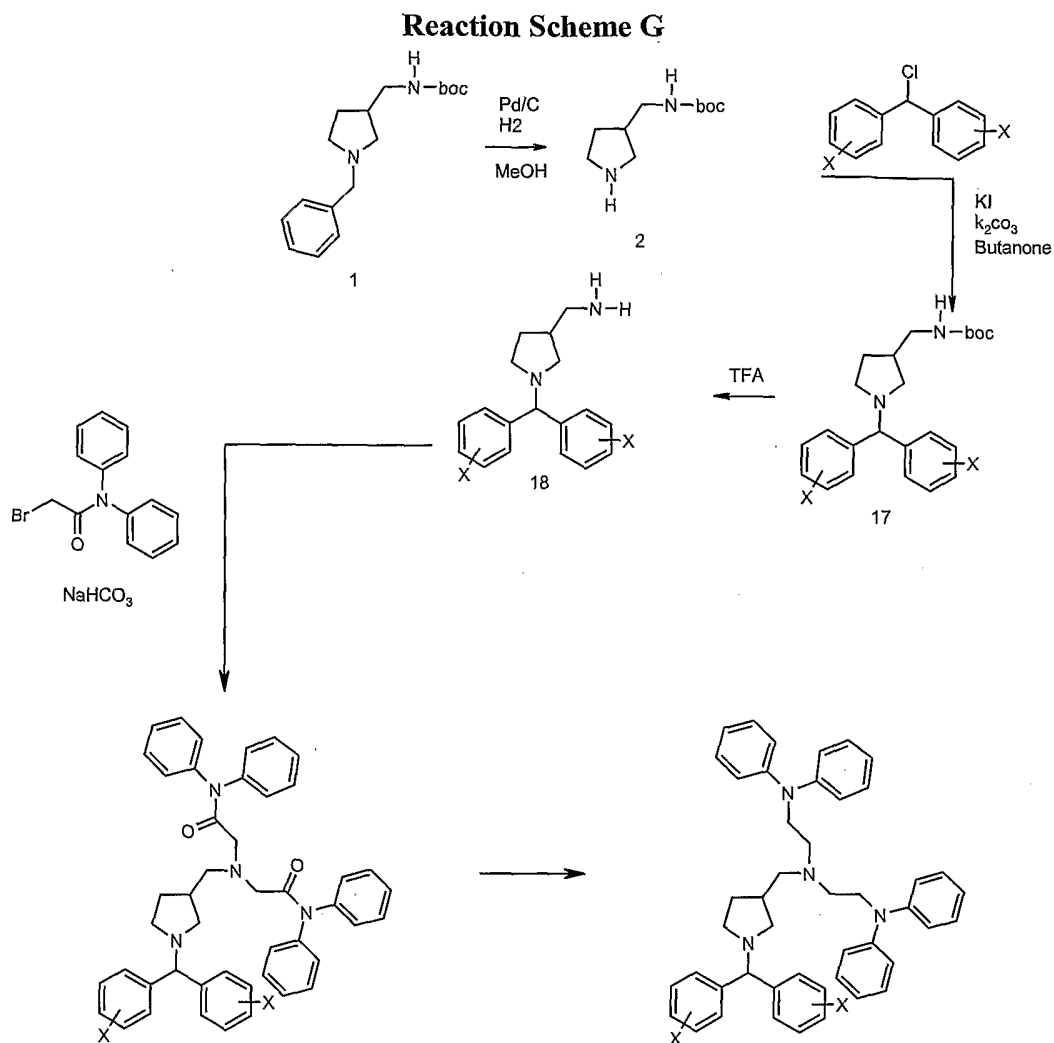


[0066] Compounds of the invention may also be synthesized using Reaction Scheme F.

Reaction Scheme F

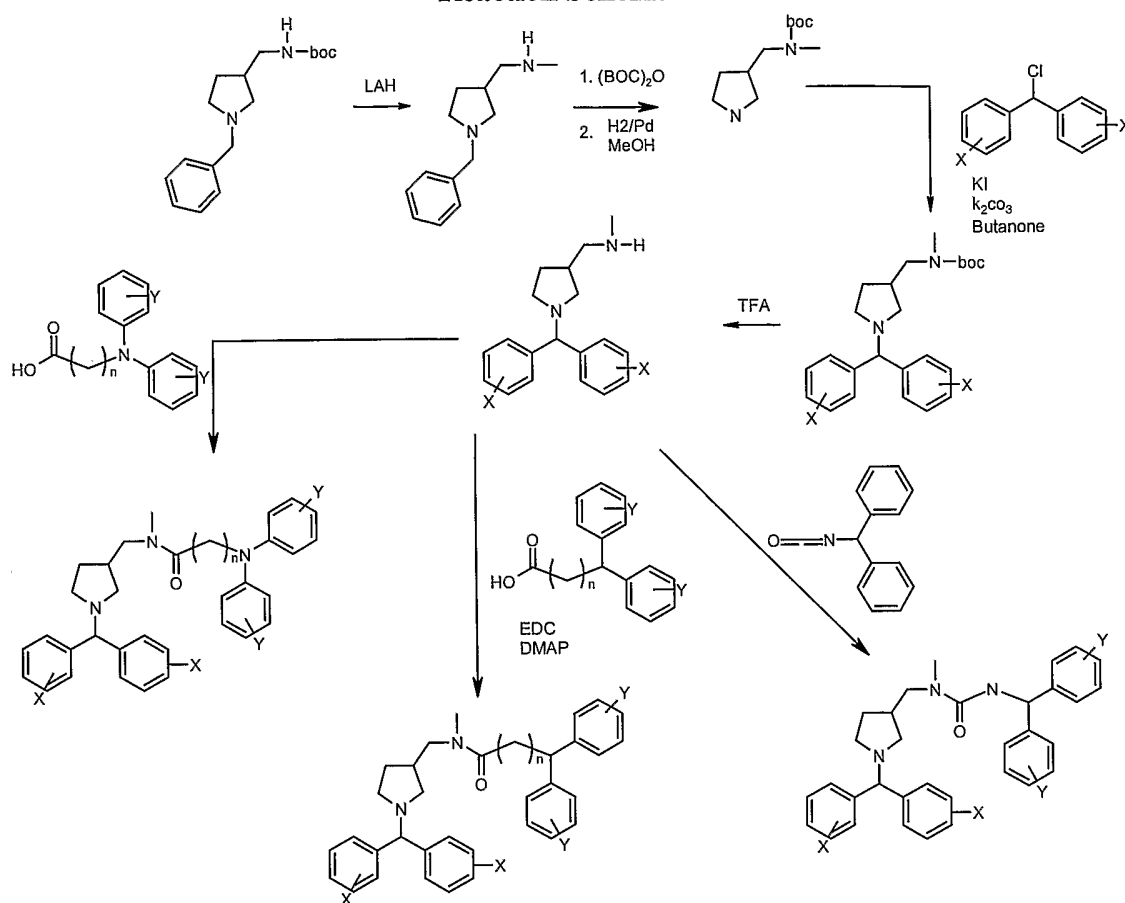


[0067] Compounds of the invention may also be synthesized using Reaction Scheme G.



[0068] Compounds of the invention may also be synthesized using Reaction Scheme H.

Reaction Scheme H

Preferred Embodiments

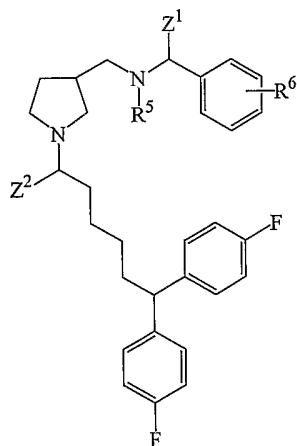
[0069] The compounds of formulas (1) and (2) are defined as shown in terms of the embodiments of their various substituents:

[0070] Particularly preferred embodiments of the compounds of formulas (1) and (2) are those wherein in CR⁴A₂ both A are phenyl; also included, however, are instances where one A is phenyl and the other is cyclohexyl, or both A are cyclohexyl.

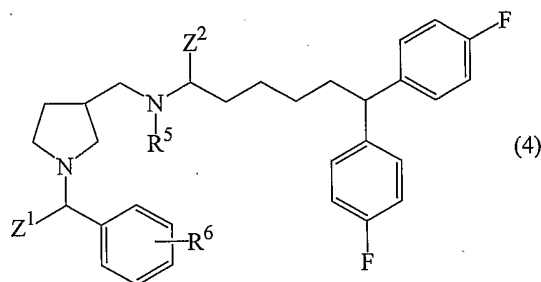
[0071] Any of the A moieties contained in the compounds of formulas (1) and (2) may be substituted, as noted above. Preferred substituents include halo, especially fluoro, alkyl (1-6C), preferably methyl or t-butyl, OR, preferably methoxy, NR₂, preferably dimethylamino, diethylamino, methylamino or ethylamino, acetamido, CF₃, OCF₃ and the like. Two substituted positions may also form a ring. Preferably, where in CR⁴A₂ where both A are phenyl, the phenyl groups are identically substituted. Where one A is phenyl and the other is cyclohexyl, the combination of at least one substituent on the phenyl and an unsubstituted cyclohexyl is preferred. It is believed that halogenation of the compounds of the invention is

helpful in modulating the *in vivo* half-life, and it may be particularly advantageous to include halogen substituents, such as fluoro substitutions on any phenyl moieties.

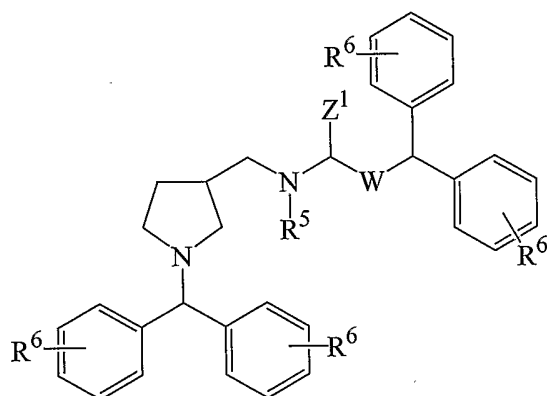
[0072] Illustrative compounds of the invention are represented by the following structures:



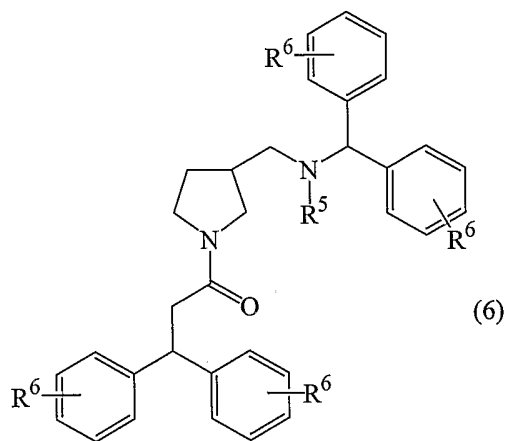
(3)



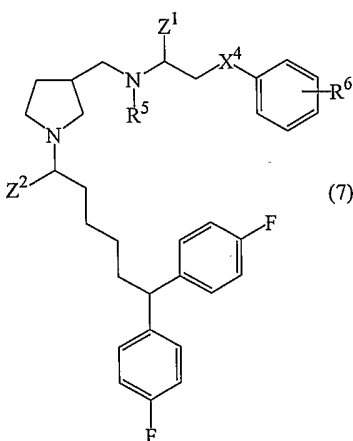
(4)



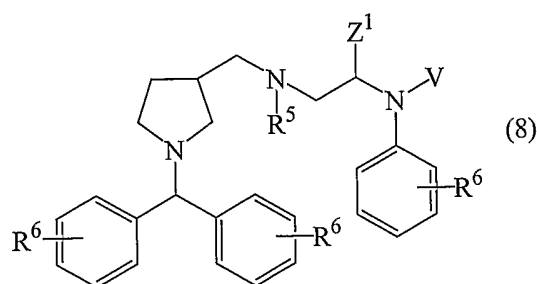
(5)



(6)



(7)



(8)

and

wherein:

each of Z^1 and Z^2 is independently either H_2 or $=O$;

$R^5 = H$, optionally substituted alkyl, $(CR_2)_nCONR^7_2$, $(CR_2)_nNR^7_2$ where each R^7 is H,

lower alkyl or aryl;

$n = 0-1$;

V is alkyl or phenyl, each optionally substituted;

W is CR₂ or NR;

X⁴ = O, S, N or NCO; and

each of R⁶ represents 0-3 substituents wherein the substituents are independently halo, CF₃, OCF, alkyl of 1-6C, aryl of (6-10C) or arylalkyl (7-16C) each optionally containing 1-4 heteroatoms (N, O, or S) and optionally substituted with inorganic substituents comprising N, P, O or S. Thus, R⁶ may include substituents, for example, that are NO₂, NR₂, OR, SR, COR, COOR, CONR₂, NROCR, or OOCR, where each R = H or lower alkyl (1-4C). Two substituents may form a 3-7 member ring optionally containing a heteroatom (N,S,O).

[0073] The pattern of substitution will influence the strength of calcium channel blocking ability as well as specificity.

Libraries and Screening

[0074] The compounds of the invention can be synthesized individually using methods known in the art per se, or as members of a combinatorial library.

[0075] Synthesis of combinatorial libraries is now commonplace in the art. Suitable descriptions of such syntheses are found, for example, in Wentworth, Jr., P., *et al.*, *Current Opinion in Biol* (1993) 9:109-115; Salemme, F. R., *et al.*, *Structure* (1997) 5:319-324. The libraries contain compounds with various substituents and various degrees of unsaturation, as well as different chain lengths. The libraries, which contain, as few as 10, but typically several hundred members to several thousand members, may then be screened for compounds which are particularly effective against a specific subtype of calcium channel, *i.e.*, the N-type channel. In addition, using standard screening protocols, the libraries may be screened for compounds which block additional channels or receptors such as sodium channels, potassium channels and the like.

[0076] Methods of performing these screening functions are well known in the art. Typically, the receptor 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 receptor 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.

[0077] 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. 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. 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.

[0078] 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. 0.067 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.

Utility and Administration

[0079] 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.

[0080] In general, for use in treatment, the compounds of formulas (1) and (2) may be used alone, as mixtures of two or more compounds of formulas (1) and (2) or in combination with other pharmaceuticals. Depending on the mode of administration, the compounds will be formulated into suitable compositions to permit facile delivery.

[0081] 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.

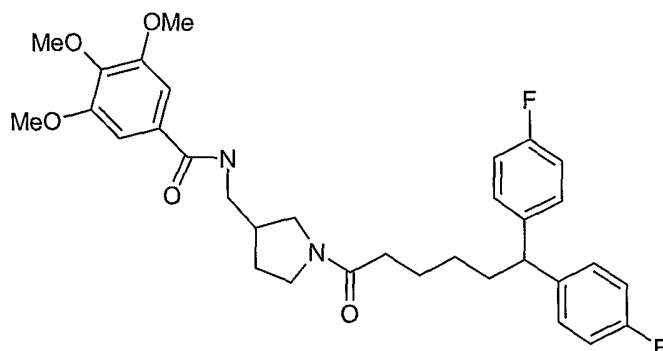
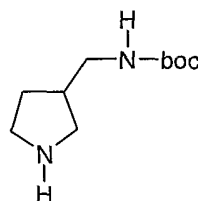
[0082] For injection, formulations can be prepared in conventional forms as liquid solutions or suspensions or as solid forms suitable for solution or suspension in liquid prior to injection or as emulsions. Suitable excipients include, for example, water, saline, dextrose, glycerol and the like. Such 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.

[0083] Various sustained release systems for drugs have also been devised. See, for example, U.S. Pat. No. 5,624,677.

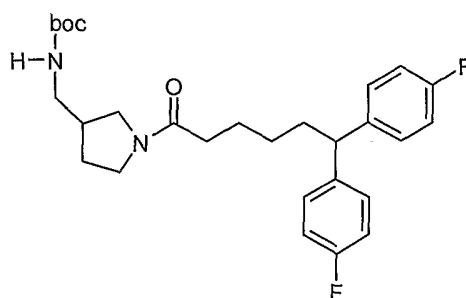
[0084] Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds of the invention. Suitable forms include syrups, capsules, tablets, as is understood in the art.

[0085] For administration to animal or human subjects, the dosage of the compounds of the invention is typically 0.1-15 mg/kg, preferably 0.1-1 mg/kg. However, dosage levels are highly dependent on the nature of the condition, drug efficacy, the condition of the patient, the judgment of the practitioner, and the frequency and mode of administration.

[0086] The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1Synthesis of N-{1-[6,6-bis-(4-fluorophenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,4,5-trimethoxy-benzamideA. Synthesis of 3-aminomethyl-3-tert-butoxycarbonylpyrrolidine

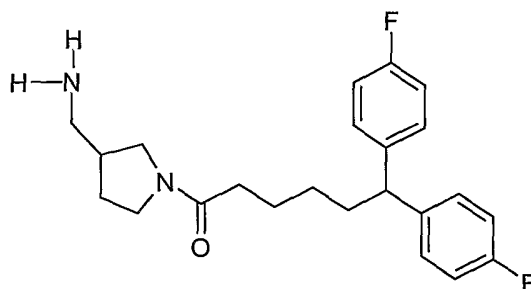
[0087] To a solution of (1-benzyl-pyrrolidin-3-ylmethyl)-carbamic acid tert-butyl ester (1) (3.0 g, 10.33 mmol) in CH₃OH (100 ml) was added Pd/C 20% (0.5 g). The resulting slurry was hydrogenated at 50 psi for 24 hours. The catalyst was filtered through Celite and filtrate evaporated under reduced pressure to give 2.0 g of desired product.

B. Synthesis of {1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-carbamic acid tert-butyl ester

[0088] To a solution of 3-aminomethyl-3-tert-butoxycarbonylpyrrolidine (0.73 g, 3.65 mmol) in dry CH₂Cl₂ (40 ml) was added 5,5-bis-(4-fluorophenyl)-hexanoic acid (1.10 g, 3.65 mmol) under nitrogen. To the reaction was added EDC (1.4 g, 7.29 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The

reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (150 ml). The organic was washed with water (30 ml, 2x) and 10% NaOH (30 ml) and dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (15:1) to give 1.6 g of desired product.

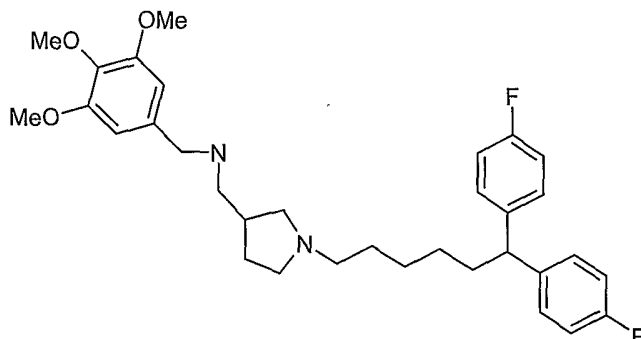
C. Synthesis of 1-(3-aminomethyl-pyrrolidin-1-yl)-6,6-bis-(4-fluoro-phenyl)-hexan-1-one



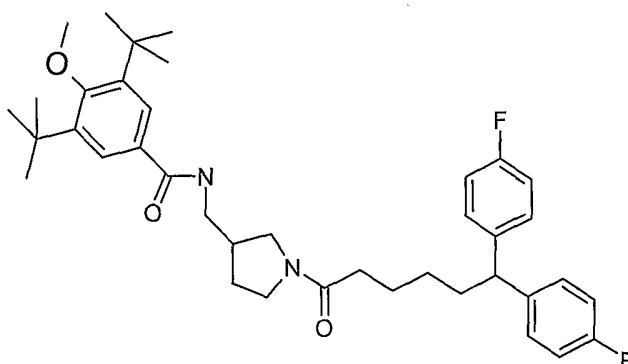
[0089] 1-[6,6-bis-(4-Fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-carbamic acid tert-butyl ester (1.6 g, 3.29 mmol) was dissolved in dry CH_2Cl_2 (50ml) followed by addition of TFA (20 ml). The resulting solution was stirred at room temperature for 2 hours. The solution was concentrated under reduced pressure. The resulting residue was dissolved in water (20 ml) and pH of the solution was adjusted to 10. The water phase was extracted with CH_2Cl_2 (100 ml), and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the desired product in almost quantitative yield.

D. Final Product

[0090] To a solution of 1-(3-aminomethyl-pyrrolidin-1-yl)-6,6-bis-(4-fluoro-phenyl)-hexan-1-one (0.69 g, 1.78 mmol) in dry CH_2Cl_2 (40 ml) was added 3,4,5-trimethoxy benzoic acid (0.38 g, 1.78 mmol) under nitrogen. To the reaction was added EDC (0.68 g, 3.56 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (150 ml). The organic was washed with water (30 ml, 2x) and 10% NaOH (30 ml) and dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (15:1) to give a desired product in good yield

EXAMPLE 2Synthesis of N-{1-[6,6-bis-(4-fluorophenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,4,5-trimethoxy-benzamide

[0091] To solution of N-{1-[6,6-bis-(4-fluorophenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,4,5-trimethoxy-benzamide (0.75 g, 1.29 mmol) in dry THF (50 ml) was added LiAlH₄ (196 mg, 5.16 mmol) under nitrogen. The resulting suspension was stirred at room temperature for 24 hours. The reaction was quenched with EtOAc (15 ml) and extracted with water (20 ml, 2x) and 10% NaOH (20 ml), dried over MgSO₄ and evaporated. The resulting residue was purified by column chromatography using CH₂Cl₂:CH₃OH (15:1) to give 0.5 g of desired product.

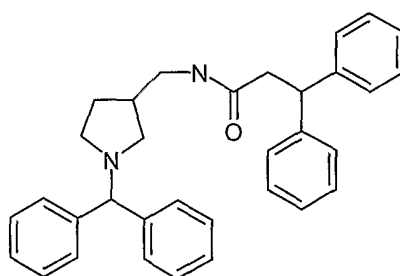
EXAMPLE 3Synthesis of N-{1-[6,6-bis-(4-fluorophenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide

[0092] To a solution of 1-(3-aminomethyl-pyrrolidin-1-yl)-6,6-bis-(4-fluoro-phenyl)-hexan-1-one (0.49 g, 1.26 mmol) in dry CH₂Cl₂ (35 ml) was added 3,5-di-tert-butyl-4-methoxy benzoic acid (0.33 g, 1.26 mmol) under nitrogen. To the reaction was added EDC (0.48 g, 2.52 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room

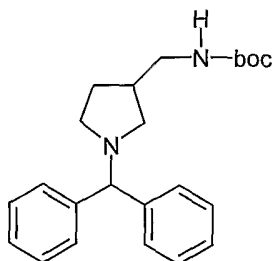
temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (130 ml). The organic was washed with water (30 ml, 2x) and 10% NaOH (30 ml) and dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (15:1) to give a desired product in good yield.

EXAMPLE 4

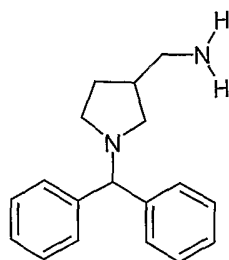
Synthesis of N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-3,3-diphenyl-propionamide



A. Synthesis of N-[1-benzhydryl]-3-aminomethyl-3-tert-butoxycarbonylpyrrolidine



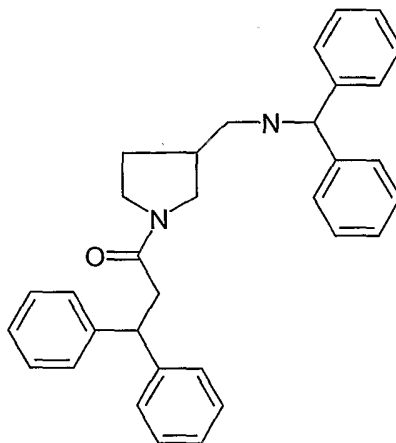
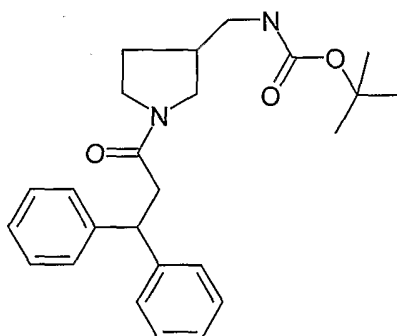
[0093] To a solution of chlorodiphenylmethane (0.68 g, 3.39 mmol) in butanone (15 ml) was added 3-aminomethyl-3-tert-butoxycarbonylpyrrolidine (0.68 g, 3.39 mmol), K_2CO_3 (0.56 g, 4.07 mmol) and KI (0.56, 3.39 mmol). The mixture was heated under reflux for 18 hours, then filtered and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml) and washed with water (10 ml). Drying over MgSO_4 and removal of solvent under reduced pressure followed by column chromatography using Hex:EtOAc (3:1) gives the desired product.

B. Synthesis of C-(1-Benzhydryl-pyrrolidin-3-yl)-methanamine

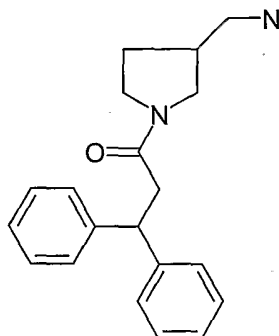
[0094] N-[1-Benzhydryl]-3-aminomethyl-3-tert-butoxycarbonylpyrrolidine (0.47 g, 1.28 mmol) was dissolved in dry CH_2Cl_2 (15 ml) followed by addition of TFA (8 ml). The resulting solution was stirred at room temperature for 2 hours. The solution was concentrated under reduced pressure. The resulting residue was dissolved in water (12 ml) and pH of the solution was adjusted to 10. The water phase was extracted with CH_2Cl_2 (100 ml), and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the desired product in almost quantitative yield.

C. Final Product

[0095] To a solution of C-(1-Benzhydryl-pyrrolidin-3-yl)-methanamine (0.26 g, 0.98 mmol) in dry CH_2Cl_2 (25 ml) was added 3,3-diphenylpropionic acid (0.22 g, 0.98 mmol) under nitrogen. To the reaction was added EDC (0.37 g, 1.95 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (100 ml). The organic was washed with water (20 ml, 2x) and 10% NaOH (20 ml) and dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using CH_2Cl_2 : CH_3OH (15:1) to give a desired product in good yield

EXAMPLE 5Synthesis of 1-{3-[Benzhydryl-amino)-methyl]-pyrrolidin-1-yl}-3,3-diphenyl-propan-1-oneA. Synthesis of [1-(3,3-Diphenyl-propionyl)-pyrrolidin-3-ylmethyl-carbamic acid tert-butyl ester]

[0096] To a solution of 3-aminomethyl-3-tert-butoxycarbonylpyrrolidine (0.6 g, 2.99 mmol) in dry CH_2Cl_2 (30 ml) was added 3,3 diphenylpropionic acid (0.68 g, 2.99 mmol) under nitrogen. To the reaction was added EDC (1.15 g, 5.99 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (100 ml). The organic was washed with water (20 ml, 2x) and 10% NaOH (20 ml) and dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using CH_2Cl_2 : CH_3OH (15:1) to give 1.0 g of desired product.

B. Synthesis of 1-(3-Aminomethyl-pyrrolidin-1-yl)-3,3-diphenyl-propan-1-one

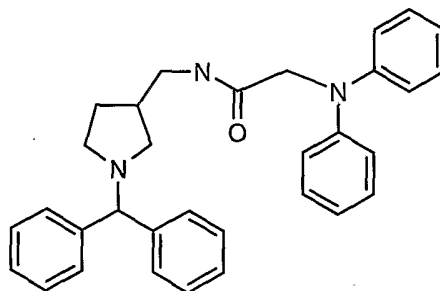
[0097] [1-(3,3-Diphenyl-propionyl)-pyrrolidin-3-ylmethy-carbamic acid tert-butyl ester (1.04 g, 2.54 mmol) was dissolved in dry CH_2Cl_2 (15 ml) followed by addition of TFA (10 ml). The resulting solution was stirred at room temperature for 2 hours. The solution was concentrated under reduced pressure. The resulting residue was dissolved in water (15 ml) and pH of the solution was adjusted to 10. The water phase was extracted with CH_2Cl_2 (100 ml), and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the desired product in almost quantitative yield

C. Final Product

[0098] A solution of 1-(3-aminomethyl-pyrrolidin-1-yl)-3,3-diphenyl-propan-1-one (0.91 g, 2.95 mmol) and benzophenone (0.22 g, 1.18 mmol) was refluxed in benzene (20 ml) in the presence of p-toluenesulfonic acid (cat.) in a Dean-Stark overnight. Benzene was then removed and the residue extracted with EtOAc (40 ml). The organic phase was then washed with water (20 ml) and dried over MgSO_4 . Removal of the solvent gave 0.9 g of crude intermediate which then dissolved in EtOH (15 ml) and NaBH_4 (0.93 g, 24.7 mmol) was gradually added to stirred solution. The reaction mixture was stirred overnight. EtOH was evaporated and residue was extracted with EtOAc, washed with water and dried. The resulting residue was purified by column chromatography using $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (15:1) to give desired product in 65% yield.

EXAMPLE 6

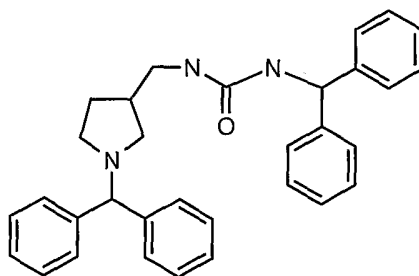
Synthesis of N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-2-diphenylamino-acetamide



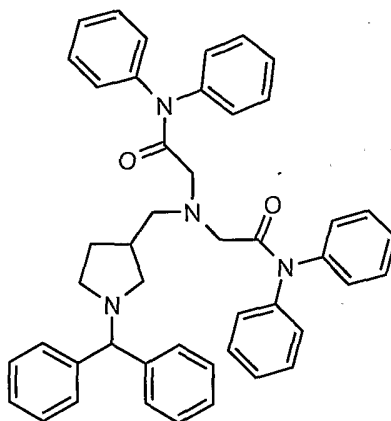
[0099] To a solution of C-(1-benzhydryl-pyrrolidin-3-yl)-methylamine (0.26 g, 0.97 mmol) in dry CH_2Cl_2 (20 ml) was added diphenylaminoacetic acid (0.22 g, 0.97 mmol) under nitrogen. To the reaction was added EDC (0.37 g, 1.95 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (100 ml). The organic was washed with water (25 ml, 2x) and 10% NaOH (25 ml) and dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using hexane:ethyl acetate (3:1) to give the desired product in 75% yield.

EXAMPLE 7

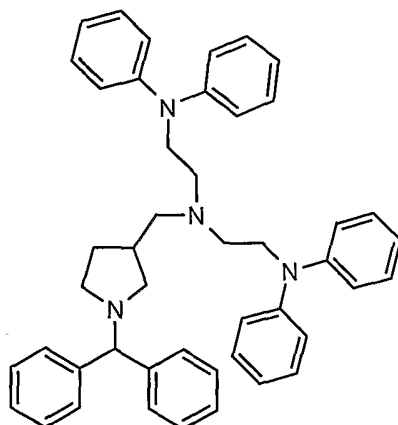
Synthesis of 1-Benzhydryl-3-(1-benzhydryl-pyrrolidin-3-ylmethyl)-urea



[00100] To a solution of C-(1-benzhydryl-pyrrolidin-3-yl)-methylamine (0.26 g, 0.97 mmol) in dry CH_2Cl_2 (5 ml) was added diphenylmethyl isocyanate (0.18 ml, 0.97 mmol) drop wise under nitrogen. The resulting mixture was stirred at room temperature over night. Removal of solvent under reduced pressure followed by column chromatography using CH_2Cl_2 : CH_3OH (20:1) gives the desired product in 80% yield.

EXAMPLE 8Synthesis of 2-[(1-Benzhydryl-pyrrolidin-3-yl)methyl]-[(diphenylcarbamoyl)-methyl]-amino}-N,N-diphenyl-acetamide

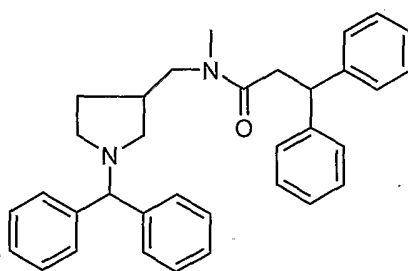
[0100] To a solution of C-(1-benzhydryl-pyrrolidin-3-yl)-methylamine (0.26 g, 0.97 mmol) in dry CH₃CN (10 ml) was added 2-bromo-N,N-diphenyl acetamide (0.56 g, 1.94 mmol) and NaHCO₃ (0.17 g, 1.95 mmol) under nitrogen. The reaction mixture was refluxed over night. After cooling, the solvent was evaporated and residue was taken up with water (5 ml) and extracted with CHCl₃ (3 x 25 ml). The organic was dried over MgSO₄ and evaporated to dryness. The resulting residue was purified by column chromatography using CH₂Cl₂:CH₃OH (15:1) to give the desired product in 82% yield.

EXAMPLE 9Synthesis of N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-N-(2-diphenylamino-ethyl)-N',N'-diphenyl-ethane-1,2-diamine

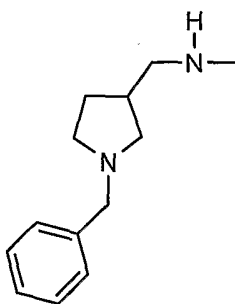
[0101] To a solution of 2-[(1-benzhydryl-pyrrolidin-3-ylmethyl)-[(diphenylcarbamoyl)-methyl]-amino]-N,N-diphenyl-acetamide (0.39 g, 0.57 mmol) in dry THF (10 ml) was added BH_3 -THF (2.5 ml, 2.29 mmol) slowly. The reaction mixture was then refluxed overnight. It was then cooled and methanol was added slowly to decompose excess BH_3 . Solvent removed and 10% HCl in methanol (20 ml) was added and refluxed for 1 hr. Cooled and solid NaHCO_3 added until neutral. Methanol was removed and extracted with ethyl acetate. The organic was dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using hexane:ethyl acetate (11:1) to give the desired product in 80% yield.

EXAMPLE 10

Synthesis of N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-N-methyl-3,3-diphenyl-propionamide

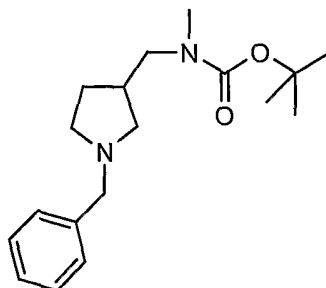


A. Synthesis of (1-Benzyl-pyrrolidin-3-ylmethyl)-methyl-amine



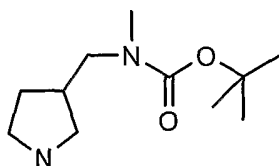
[0102] To a cooled (-5°C) and stirred solution of LAH (1 M, 7.6 ml) in dry THF (75 ml) was added a solution of (1-benzyl-pyrrolidin-3-ylmethyl)-carbamic acid tert-butyl ester (1.47 g, 5.06 mmol) in THF (22 ml) over 20 minutes. The mixture was then heated at reflux for 2.5 hrs and cooled to room temperature and quenched by successive addition of ethyl acetate (50 ml). The organic layer was then washed with water (2X), 10% NaOH and brine, dried and evaporated to give the desired product in 90% yield.

B. Synthesis of (1-benzyl-pyrrolidin-3-ylmethyl)-carbamic acid tert-butyl ester methyl amine



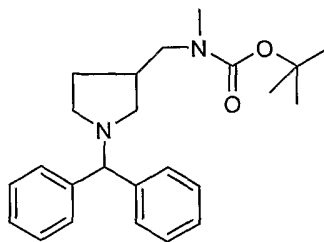
[0103] A solution of (1-benzyl-pyrrolidin-3-ylmethyl)- methyl amine (1.03 g, 5.04 mmol) in THF (30 ml), water (1 ml) and NaOH (0.5 ml) was cooled to 0°C. (BOC)₂O (1.32 g, 6.05 mmol) was then added and reaction was stirred at room temperature for 2 hrs. The solvent was evaporated and the residue was partitioned between 2N aq. NaOH and CH₂Cl₂. The organic phase was washed with brine, dried and evaporated to dryness to give the desired product in 92% yield.

C. Synthesis of (Methyl-pyrrolidine-3-ylmethyl-amine)- carbamic acid tert-butyl ester



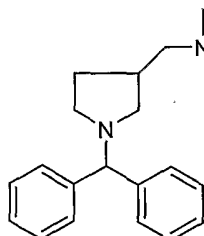
[0104] To a solution of (1-benzyl-pyrrolidin-3-ylmethyl)-carbamic acid tert-butyl ester methyl amine (1.0 g, 3.28 mmol) in methanol (35 ml) was added Pd/C (20%) (0.22 g). The resulting mixture was hydrogenated at 50 Psi over night. The Pd was filtered over Celite and evaporated to dryness to give the desired product in 92% yield.

D. Synthesis of (1-Benzhydryl-pyrrolidin-3-ylmethyl)-methyl-carbamic acid tert-butyl ester



[0105] To a solution of chlorodiphenylmethane (0.79 g, 3.22 mmol) in butanone (20 ml) was added methyl-pyrrolidine-3-ylmethyl-amine)- carbamic acid tert-butyl ester (0.69 g, 3.22 mmol), K_2CO_3 (0.54 g, 3.8 mmol) and KI (0.54 g, 3.22 mmol). The mixture was heated under reflux for 18 hours, then filtered and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml) and washed with water (10 ml). Drying over $MgSO_4$ and removal of solvent under reduced pressure followed by column chromatography using $CH_2Cl_2:CH_3OH$ (20:1) gives the desired product in 75% yield.

E. Synthesis of (1-Benzhydryl-pyrrolidin-3-ylmethyl)-methyl-amine



[0106] (1-Benzhydryl-pyrrolidin-3-ylmethyl)methyl carbamic acid-tert-butyl ester (0.47 g, 1.67 mmol) was dissolved in dry CH_2Cl_2 (15 ml) followed by addition of TFA (8 ml). The resulting solution was stirred at r.t. for 2 hrs. The solution was concentrated under reduced pressure. The resulting residue was dissolved in water (12 ml) and pH of the solution was adjusted to 10. The water phase was extracted with CH_2Cl_2 (100 ml), and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the desired product in almost quantitative yield.

F. Synthesis of final product

[0107] To a solution of (1-benzhydryl pyrrolidin-3-ylmethyl)-methyl amine (0.31 g, 1.10 mmol) in dry CH_2Cl_2 (25 ml) was added 3,3-diphenylpropionic acid (0.25 g, 1.10 mmol)

under nitrogen. To the reaction was added EDC (0.42 g, 2.2 mmol) and DMAP (cat) and the reaction mixture stirred under nitrogen at room temp. overnight. The reaction was then concentrated under reduced pressure. The residue dissolved in ethyl acetate: water (10:1) (100 ml). The organic was washed with water (20 ml, 2x) and 10% NaOH (20 ml) and dried over MgSO_4 and evaporated to dryness. The resulting residue was purified by column chromatography using $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (15:1) to give a desired product in good yield.

EXAMPLE 11

Assessment of Calcium Channel Blocking Activity

[0108] Antagonist activity was measured using whole cell patch recordings on human embryonic kidney cells either stably or transiently expressing rat $\alpha_{1B} + \alpha_{2\delta} + \beta_{1b}$ channels (N-type channels) with 5 mM barium as a charge carrier. P/Q-type channels ($\alpha_{1A} + \alpha_{2\delta} + \beta_{1b}$ cDNA subunits) and L-type channels ($\alpha_{1C} + \alpha_{2\delta} + \beta_{1b}$ cDNA subunits) were also transiently expressed in HEK 293 cells.

[0109] For transient expression, host cells, such as human embryonic kidney cells, HEK 293 (ATCC# CRL 1573) were grown in standard DMEM medium supplemented with 2 mM glutamine and 10% fetal bovine serum. HEK 293 cells were transfected by a standard calcium-phosphate-DNA coprecipitation method using the rat $\alpha_{1B} + \beta_{1b} + \alpha_{2\delta}$ N-type calcium channel subunits in a vertebrate expression vector (for example, see Current Protocols in Molecular Biology).

[0110] After an incubation period of from 24 to 72 hrs the culture medium was removed and replaced with external recording solution (see below). Whole cell patch clamp experiments were performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, Calif.) linked to an IBM compatible personal computer equipped with pCLAMP software. Borosilicate glass patch pipettes (Sutter Instrument Co., Novato, Calif.) were polished (Microforge, Narishige, Japan) to a resistance of about 4 M Ω when filled with cesium methanesulfonate internal solution (composition in mM: 109 CsCH₃ SO₄, 4 MgCl₂, 9 EGTA, 9 HEPES, pH 7.2). Cells were bathed in 5 mM Ba⁺⁺ (in mM: 5 BaCl₂, 1 MgCl₂, 10 HEPES, 40 tetraethylammonium chloride, 10 glucose, 87.5 CsCl pH 7.2). Current data shown were elicited by a train of 100 ms test pulses at 0.066 Hz from -100 mV and/or -80 mV to various potentials (min. -20 mV, max. +30 mV). Drugs were perfused directly into the vicinity of the cells using a microperfusion system.

[0111] Normalized dose-response curves were fit (Sigmaplot 4.0, SPSS Inc., Chicago, Ill.) by the Hill equation to determine IC_{50} values. Steady-state inactivation curves were plotted as the normalized test pulse amplitude following 5 s inactivating prepulses at +10 mV increments. Inactivation curves were fit (Sigmaplot 4.0) with the Boltzman equation, I_{peak} (normalized) = $1/(1+\exp((V-V_h)z/25.6))$, where V and V_h are the conditioning and half inactivation potentials, respectively, and z is the slope factor.

[0112] Figure 1 is a graph that shows the selectivity of compound P13 for N-type calcium channels over L-type and P/Q-type channels. P13 is approximately 21-fold more selective for N-type over P/Q-type channels and greater than 100-fold selective for N-type over L-type channels.

[0113] Figure 2 is a graph that shows the selectivity of compound P17 for N-type calcium channels over L-type and P/Q-type channels. P17 is approximately 31-fold more selective for N-type over P/Q-type channels and greater than 75-fold selective for N-type over L-type channels.

EXAMPLE 12

N-type Channel Blocking Activities of Various Invention Compounds

[0114] The methods of Examples 1 and 2 were followed with slight modifications as will be apparent from the description below.

A. Transformation of HEK cells:

[0115] 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% CO₂. 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% CO₂. Cells were incubated for 1 to 2 days to whole cell recording.

B. Measurement of Inhibition

[0116] 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 BaCl₂, 10 mM MgCl₂, 10 mM HEPES, 40 mM TEACl, 10 mM glucose, 87.5 mM CsCl (pH 7.2) and 108 mM CsMS, 4 mM MgCl₂, 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).

[0117] Specific data obtained for N-type channels are shown in Table 3 below.

TABLE 3
N-type Calcium Channel Block

Compound	IC ₅₀ at 0.067 Hz (nM)	IC ₅₀ at 0.2 Hz (nM)
P1	61	Not tested
P2	1070	840
P3	417	Not tested
P4	400	Not tested
P5	59	Not tested
P6	212	Not tested
P7	49	Not tested
P8	35	Not tested
P9	15	Not tested
P11	10	Not tested
P12	32	Not tested
P13	41	Not tested
P14	39	Not tested
P15	>1000	Not tested
P17	60	Not tested
P18	28	Not tested
P19	250	94
P20	450	280
P21	210	150
P23	410	200

Compound	IC ₅₀ at 0.067 Hz (nM)	IC ₅₀ at 0.2 Hz (nM)
P24	380	210
P25	110	78
P26	263	236
P31	563	220
P36	100	20
P37	23	8
P38	80	24
P39	179	257
P40	19	3
P41	485	149
P42	618	356
P43	266	159
P44	265	119
P45	512	247
P46	7	1
P47	295	185
P48	133	99
P49	136	89
P50	76	53
P51	72	56
P52	135	110
P53	223	157
P54	279	241
P55	326	226
P56	137	92
P57	225	81
P58	120	86
P59	8000	2000
P60	57	45
P63	380	330

EXAMPLE 13

T-type Channel Blocking Activities of Various Invention Compounds

[0118] Standard patch-clamp techniques were employed to identify blockers of T-type currents. Briefly, previously described HEK cell lines stably expressing human α_{1G} T-type channels were used for all the recordings (passage #: 4-20, 37°C, 5% CO₂). To obtain T-type currents, plastic dishes containing semi-confluent cells were positioned on the stage of a ZEISS AXIOVERT S100 microscope after replacing the culture medium with external solution (see

below). Whole-cell patches were obtained using pipettes (borosilicate glass with filament, O.D.: 1.5 mm, I.D.: 0.86 mm, 10 cm length), fabricated on a SUTTER P-97 puller with resistance values of ~5 M Ω (see below for internal solution).

TABLE 4
External Solution 500 ml – pH 7.4, 265.5 mOsm

<i>Salt</i>	<i>Final mM</i>	<i>Stock M</i>	<i>Final ml</i>
CsCl	132	1	66
CaCl ₂	2	1	1
MgCl ₂	1	1	0.5
HEPES	10	0.5	10
glucose	10	-----	0.9 grams

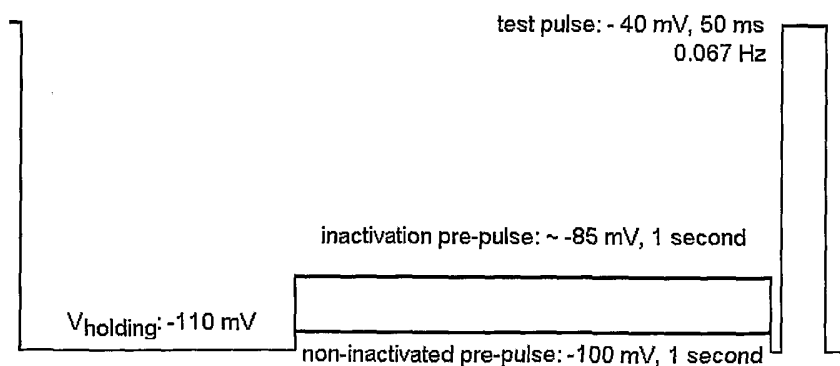
TABLE 5
Internal Solution 50 ml – pH 7.3 with CsOH, 270 mOsm

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

T-type currents were reliably obtained by using two voltage protocols:

- (1) “non-inactivating”, and
- (2) “inactivation”

[0119] In the non-inactivating protocol, the holding potential is set at –110 mV and with a pre-pulse at –100 mV for 1 second prior to the test pulse at –40 mV for 50 ms. In the inactivation protocol, the pre-pulse is at approximately –85 mV for 1 second, which inactivates about 15% of the T-type channels.



[0120] Test compounds were dissolved in external solution, 0.1-0.01 % DMSO. After ~10 min rest, they were applied by gravity close to the cell using a WPI microfil tubing. The “non-

inactivated” pre-pulse was used to examine the resting block of a compound. The “inactivated” protocol was employed to study voltage-dependent block. However, the initial data shown below were mainly obtained using the non-inactivated protocol only. IC₅₀ values are shown for various compounds of the invention in Table 6.

Table 6
Block of α_{1G} T-type Channels

Compound	IC ₅₀ at -100 mV (nM)	IC ₅₀ at -80 mV (nM)
P2	326	52
P3	86	Not tested
P5	No effect	Not tested
P11	27	Not tested
P13	1.5	0.7
P15	>10,000	Not tested
P17	29	Not tested
P19	70	Not tested
P24	12	Not tested
P26	137	42
P31	460	196
P36	30	12
P37	111	28
P38	94	21
P39	12	3
P40	328	105
P41	21	6
P42	94	59
P43	48	15
P44	52	29
P45	410	67
P46	23	5
P47	24	8
P48	4.8	1.9
P49	18	8
P54	153	55
P55	57	18
P57	115	28
P58	79	58
P59	40000	6000
P60	618	227

EXAMPLE 14Activity of Invention Compounds in Formalin-Induced Pain Model

[0121] The effects of intrathecally delivered compounds of the invention on the rat formalin model were measured. The compounds were reconstituted to stock solutions of approximately 10 mg/ml in propylene glycol. Eight Holtzman male rats of 275-375 g size were randomly selected per test article.

[0122] The following study groups were used, with test article, vehicle control (propylene glycol) and saline delivered intraperitoneally (IP):

TABLE 7
Formalin Model Dose Groups

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

N/A = Not Applicable

[0123] Prior to initiation of drug delivery baseline behavioral and testing data were taken. At selected times after infusion of the Test or Control Article these data were again collected.

[0124] On the morning of testing, a small metal band (0.5 g) was loosely placed around the right hind paw. The rat was placed in a cylindrical Plexiglas chamber for adaptation a minimum of 30 minutes. Test Article or Vehicle Control Article was administered 10 minutes prior to formalin injection (50 μ l of 5% formalin) into the dorsal surface of the right hindpaw of the rat. The animal was then placed into the chamber of the automated formalin apparatus where movement of the formalin injected paw was 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).

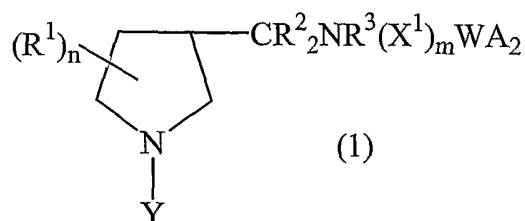
[0125] Results are presented as Maximum Possible Effect $\pm$ SEM, where saline control = 100%.

TABLE 8
Efficacy of Invention Compounds in Formalin-Induced Pain Model

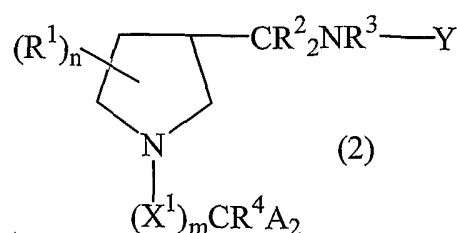
Compound	Phase I	Phase II	Phase IIA
P13	85±9	86±7	86±5
P17	74±8	84±9	79±9
P24	66±11	38±7	20±4

Claims

1. A compound of the formula



or



or the salts thereof, including all stereoisomeric forms thereof

wherein:

Y is $(X^2)_lA$ or $(X^1)_mCR^4A_2$;

W is CR^4 or N;

R^1 - R^4 are noninterfering substituents;

n is 0-7;

l and m are independently 0 or 1;

X^1 - X^2 are linkers;

each A is independently a 5-7 membered optionally substituted aromatic or aliphatic ring optionally containing one or more heteroatoms selected from O, N and S.

2. The compound of claim 1, wherein each R^1 is independently optionally substituted lower alkyl (1-6C), optionally substituted lower alkenyl (2-6C), or optionally substituted lower alkynyl (2-6C), each optionally including one or more heteroatoms selected from O, N and S or is an inorganic substituent.

3. The compound of claim 2, wherein each R^1 and each said optional substituent is independently halo, NO_2 , SO_2 , SO, NO, =O, =NOH and n is 0-3.

4. The compound of claim 1, wherein each R^2 is independently H, lower alkyl, lower alkenyl or halo.

5. The compound of claim 4, wherein each R^2 is independently H or lower alkyl.

6. The compound of claim 5, wherein at least one R^2 is H.

7. The compound of claim 1, wherein R^3 is H, lower alkyl, lower alkenyl, or lower acyl, wherein one or more carbons of each of the foregoing is replaced with a heteroatom.
8. The compound of claim 7, wherein R^3 is H or $\text{CONCH}_2\text{CH}_3$.
9. The compound of claim 1, wherein R^4 is H, alkyl, alkenyl, arylalkyl, arylalkenyl, hydroxy, alkoxy, sulfhydryl, alkylsulfhydryl, amino or alkylamino.
10. The compound of claim 9, wherein R^4 is H, hydroxy or alkoxy.
11. The compound of claim 10, wherein R^4 is H.
12. The compound of claim 1, wherein each X^1 is independently optionally substituted alkylene or alkenylene (1-10C) wherein one or more said C may optionally be replaced by N or O.
13. The compound of claim 12, wherein said alkylene or alkenylene is unsubstituted or is substituted by =O.
14. The compound of claim 13, wherein said =O is at the carbon adjacent the nitrogen to which X^1 is coupled.
15. The compound of claim 1, wherein X^2 is independently optionally substituted alkylene (1-10C) or alkenylene (2-10C) wherein one or more said C may optionally be replaced by N or O.
16. The compound of claim 15, wherein said alkylene or alkenylene is unsubstituted or is substituted by =O.
17. The compound of claim 16, wherein said =O is at the carbon adjacent the nitrogen to which X^1 is coupled.
18. The compound of claim 1, wherein each A is independently optionally substituted phenyl, optionally substituted cyclohexyl, optionally substituted 2-, 3- or 4-pyridyl,

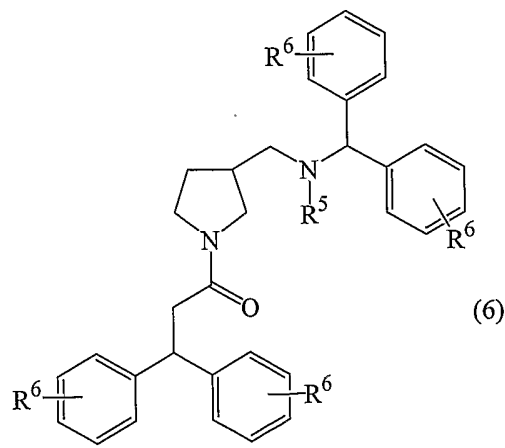
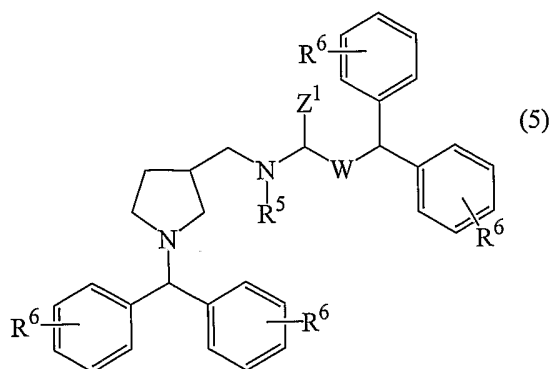
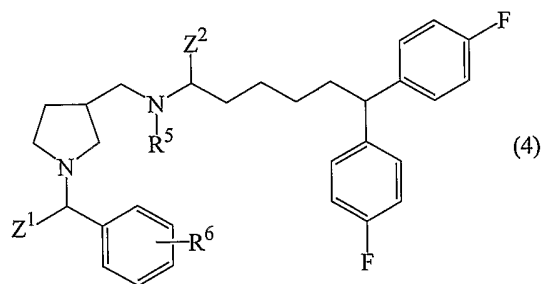
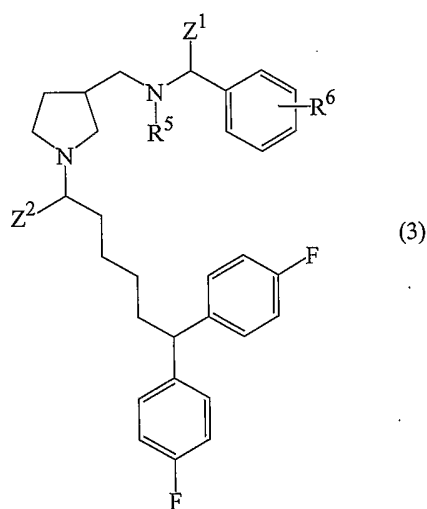
optionally substituted indolyl, optionally substituted 2- or 4-pyrimidyl, optionally substituted pyridazinyl, optionally substituted benzotriazolyl or optionally substituted benzimidazolyl.

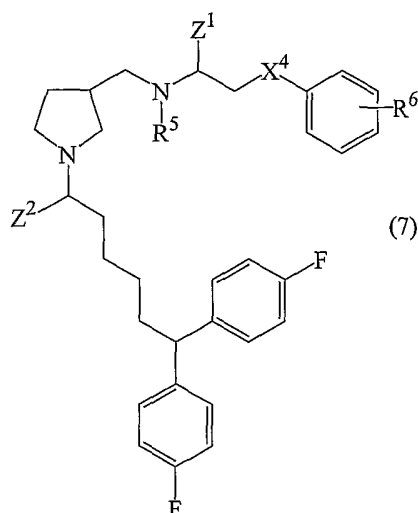
19. The compound of claim 18, wherein said substituents are alkyl, alkenyl, alkynyl, aryl, alkylaryl or alkenylaryl, in each case optionally substituted and in each case optionally containing one or more heteroatoms in place of carbon or is an inorganic substituent.

20. The compound of claim 18, wherein each A is independently phenyl, cyclohexyl, pyridyl or pyrimidyl.

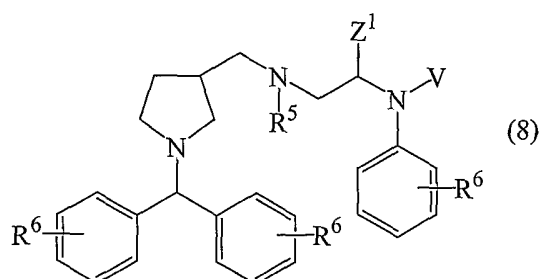
21. The compound of claim 19, wherein each of said substituents is independently halo, alkoxy or alkyl.

22. A compound of claim 1 which is of the formula





or



wherein:

each Z^1 and Z^2 is independently H_2 or $=O$;

$R^5 = H$, optionally substituted alkyl, $(CR_2)_nCONR_2^7$, $(CR_2)_nNR_2^7$ where each R^7 is H , lower alkyl or aryl;

$n = 0-1$;

V is alkyl or phenyl, each optionally substituted;

W is CR_2 or NR ;

X^4 is O , S , N or NCO ; and

R^6 represents 0-3 substituents wherein said substituents are independently alkyl (1-6C), aryl (6-10C) or arylalkyl (7-16C) each optionally containing 1-4 heteroatoms (halo, N , O , or S), and/or said substituents are halo, CF_3 , OCF , NO_2 , NR_2 , OR , SR , COR , $COOR$, $CONR_2$, $NROCR$, or $OOOCR$, wherein two substituents may form a 3-7 member ring optionally containing a heteroatom N , S or O ;

and wherein each $R = H$ or alkyl (1-8C).

23. The compound of claim 1 which is

N -(1-benzhydryl-pyrrolidin-3-ylmethyl)-3,3-diphenyl-propionamide;

1-{3-[(benzhydryl-amino)-methyl]-pyrrolidin-1-yl}-3,3-diphenyl-propan-1-one;

N -{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,4,5-trimethoxy-benzamide;

{1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-(3,4,5-trimethoxy-benzyl)-amine;

6,6-bis-(4-fluoro-phenyl)-hexanoic acid [1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-ylmethyl]-amide;

[6,6-bis-(4-fluoro-phenyl)-hexyl]-[1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-ylmethyl]-amine;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-hydroxy-benzamide;

4-[(1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl)-amino)-methyl]-2,6-di-tert-butyl-phenol;

6,6-bis-(4-fluoro-phenyl)-hexanoic acid [1-(3,5-di-tert-butyl-4-hydroxy-benzoyl)-pyrrolidin-3-ylmethyl]-amide;

4-(3-{[6,6-bis-(4-fluoro-phenyl)-hexylamino]-methyl}-pyrrolidin-1-ylmethyl)-2,6-di-tert-butyl-phenol;

6,6-bis-(4-fluoro-phenyl)-hexanoic acid [1-(3,5-di-tert-butyl-4-methoxy-benzoyl)-pyrrolidin-3-ylmethyl]-amide;

[6,6-bis-(4-fluoro-phenyl)-hexyl]-[1-(3,5-di-tert-butyl-4-methoxy-benzyl)-pyrrolidin-3-ylmethyl]-amine;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide;

{1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-(3,5-di-tert-butyl-4-methoxy-benzyl)-amine;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-dibromo-4-hydroxy-benzamide;

4-[(1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl)-amino)-methyl]-2,6-dibromo-phenol;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-benzamide;

{1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-(3,5-di-tert-butyl-benzyl)-amine;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-3,4,5-trimethoxy-benzamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-(2-dimethylamino-ethoxy)-benzamide;

6,6-bis-(4-fluoro-phenyl)-hexanoic acid {1-[3,5-di-tert-butyl-4-(2-dimethylamino-ethoxy)-benzoyl]-pyrrolidin-3-ylmethyl}-amide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-4-tert-butyl-benzamide;

N-{1-[(4-chloro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-diphenyl-propionamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-phenoxy-acetamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-phenylsulfanyl-acetamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-phenylamino-acetamide;

N-[2-({1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-amino)-ethyl]-3,4,5-trimethoxy-benzamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(2,4-difluoro-phenoxy)-acetamide;

1-(1-benzhydryl-pyrrolidin-3-ylmethyl)-1-(3,3-diphenyl-propionyl)-3-ethyl-urea;

1-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3-ethyl-1-(2-phenylsulfanyl-acetyl)-urea;

1-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3-ethyl-1-(2-phenylamino-acetyl)-urea;

1-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-1-[2-(2,4-difluoro-phenoxy)-acetyl]-3-ethyl-urea;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(4-chloro-phenoxy)-acetamide;

N-{1-[(2-chloro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-diphenyl-propionamide;

N-{1-[(3-chloro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-diphenyl-propionamide;

3,3-diphenyl-N-{1-[phenyl-(4-trifluoromethyl-phenyl)-methyl]-pyrrolidin-3-ylmethyl}-propionamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(3,5-dimethyl-phenylamino)-acetamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(3,5-dimethyl-phenylamino)-acetamide;

R-N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide;

S-N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide;

R-N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-benzamide;

S-N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-benzamide;

N-(1-benzhydryl-pyrrolidin-3-ylmethyl)-2-diphenylamino-acetamide;

2-{(1-benzhydryl-pyrrolidin-3-ylmethyl)-[(diphenylcarbamoyl)-methyl]-amino}-N,N-diphenyl-acetamide;

1-benzhydryl-3-(1-benzhydryl-pyrrolidin-3-ylmethyl)-urea;

S-N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide;

R-N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide;

3,3-bis-(4-fluoro-phenyl)-N-{1-[(4-fluoro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-propionamide;

N-(1-benzhydryl-pyrrolidin-3-ylmethyl)-3,3-bis-(4-fluoro-phenyl)-propionamide;

N-{1-[(4-tert-butyl-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-bis-(4-fluoro-phenyl)-propionamide;

N-(1-benzhydryl-pyrrolidin-3-ylmethyl)-N-methyl-3,3-diphenyl-propionamide;

2-[(1-benzhydryl-pyrrolidin-3-ylmethyl)-methyl-amino]-N,N-diphenyl-acetamide;

N-(1-benzhydryl-pyrrolidin-3-ylmethyl)-N-methyl-N',N'-diphenyl-ethane-1,2-diamine;

(1-benzhydryl-pyrrolidin-3-ylmethyl)-(3,3-diphenyl-propyl)-methyl-amine;

1-(3-{[(3,5-bis-trifluoromethyl-benzyl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-6,6-bis-(4-fluoro-phenyl)-hexan-1-one;

6,6-bis-(4-fluoro-phenyl)-1-(3-{[methyl-(3,4,5-trimethoxy-benzyl)-amino]-methyl}-pyrrolidin-1-yl)-hexan-1-one;

N-(1-benzhydryl-pyrrolidin-3-ylmethyl)-N-(2-diphenylamino-ethyl)-N',N'-diphenyl-ethane-1,2-diamine;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3-fluoro-5-trifluoromethyl-benzamide;

N-{1-[6,6-bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-4-fluoro-3-trifluoromethyl-benzamide; or

[3-({[6,6-bis-(4-fluoro-phenyl)-hexyl]-methyl-amino}-methyl)-pyrrolidin-1-yl]-(3,4,5-trimethoxy-phenyl)-methanone.

24. A method to treat conditions associated with undesired calcium channel activity in a subject which method comprises administering to a subject in need of such treatment a compound of claim 1 or a pharmaceutical composition thereof.

25. A pharmaceutical composition for use in treating conditions characterized by undesired calcium channel activity which composition comprises, in admixture with a pharmaceutically acceptable excipient, a dosage amount of the compound of claim 1.

26. A method of claim 24 where such condition is associated with N-type calcium channel activity.

27. A method of claim 26 where such condition is selected from chronic pain conditions such as neuropathic pain, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, AIDS related neuropathy, cancer pain, inflammatory pain, osteoarthritis pain, rheumatoid arthritis pain and fibromyalgia; acute pain; nociceptive pain; post-operative pain; mood disorders; anxiety disorders such as generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive compulsive disorder and post-traumatic stress syndrome; depression; addiction disorders such as cocaine dependence and withdrawal, opioid dependence and withdrawal, alcohol dependence and withdrawal and nicotine dependence and withdrawal; gastrointestinal disorders such as inflammatory bowel disease and irritable bowel

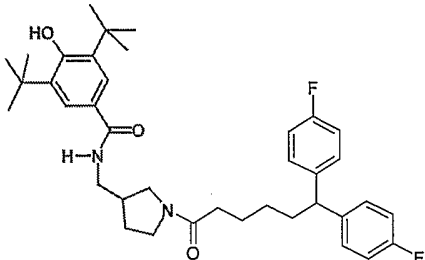
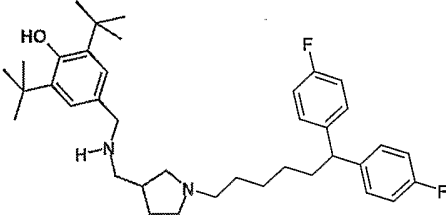
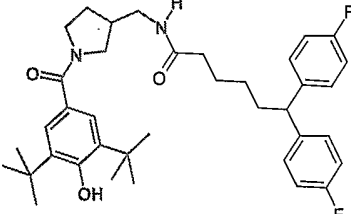
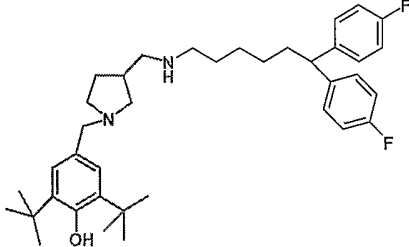
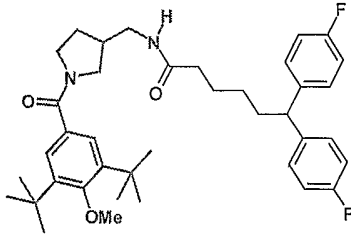
syndrome; or genitourinary disorders such as urinary incontinence, interstitial colitis and sexual dysfunction.

28. A method of claim 24 where such condition is associated with T-type calcium channel activity.

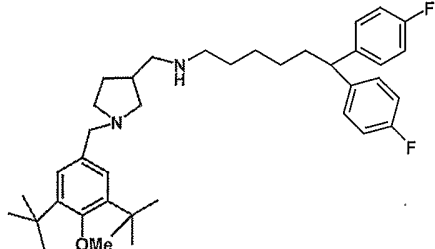
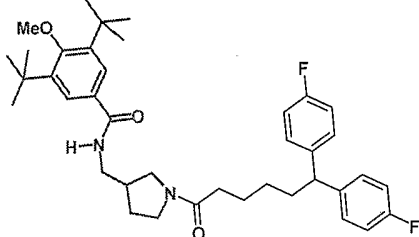
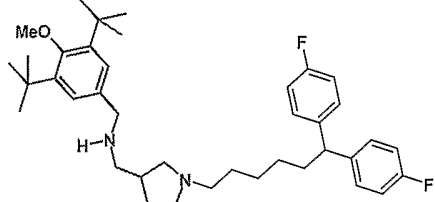
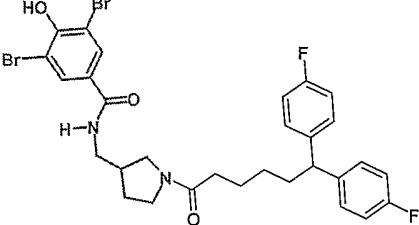
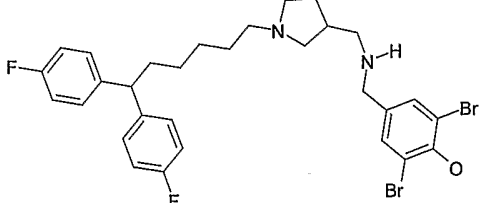
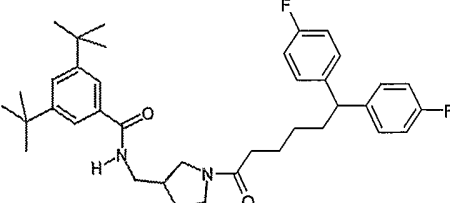
29. A method of claim 28 where such condition is selected from cardiovascular diseases such as hypertension, arrhythmias, atrial fibrillation congestive heart failure and angina pectoris; epilepsy conditions such as partial seizures, temporal lobe epilepsy, absence seizures, generalized seizures and tonic/clonic seizures; diabetes, cancer, chronic pain conditions, neuropathic pain, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, AIDS related neuropathy, cancer pain, inflammatory pain, osteoarthritis pain, rheumatoid arthritis pain and fibromyalgia; acute pain; nociceptive pain and post-operative pain.

#	Name	Structure
P1	N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-3,3-diphenyl-propionamide	
P2	1-{3-[(Benzhydryl-amino)-methyl]-pyrrolidin-1-yl}-3,3-diphenyl-propan-1-one	
P3	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,4,5-trimethoxy-benzamide	
P4	{1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-(3,4,5-trimethoxy-benzyl)-amine	
P5	6,6-Bis-(4-fluoro-phenyl)-hexanoic acid [1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-ylmethyl]-amide	
P6	[6,6-Bis-(4-fluoro-phenyl)-hexyl]-[1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-ylmethyl]-amine	

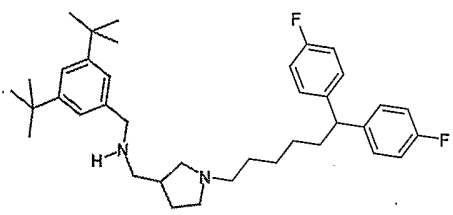
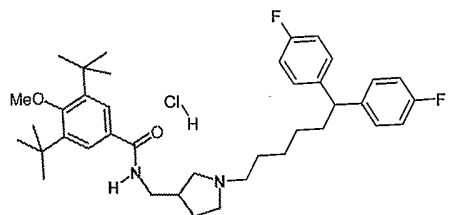
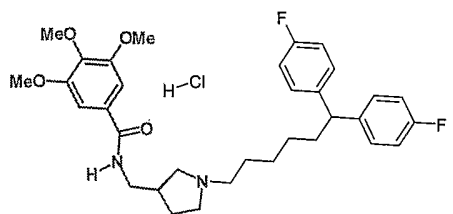
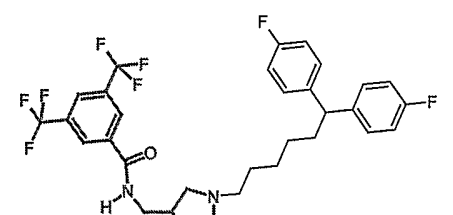
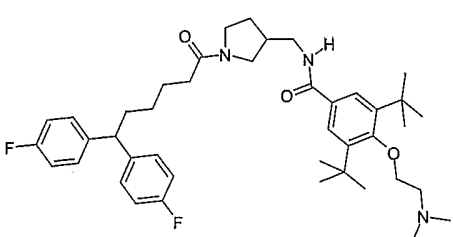
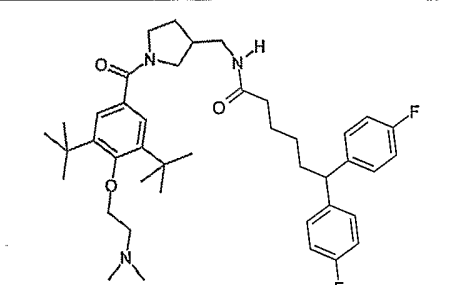
Figure 1

#	Name	Structure
P7	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-hydroxy-benzamide	
P8	4-[(1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl)-amino]-methyl]-2,6-di-tert-butyl-phenol	
P9	6,6-Bis-(4-fluoro-phenyl)-hexanoic acid [1-(3,5-di-tert-butyl-4-hydroxy-benzoyl)-pyrrolidin-3-ylmethyl]-amide	
P10	4-(3-{[6,6-Bis-(4-fluoro-phenyl)-hexylamino]-methyl}-pyrrolidin-1-ylmethyl)-2,6-di-tert-butyl-phenol	
P11	6,6-Bis-(4-fluoro-phenyl)-hexanoic acid [1-(3,5-di-tert-butyl-4-methoxy-benzoyl)-pyrrolidin-3-ylmethyl]-amide	

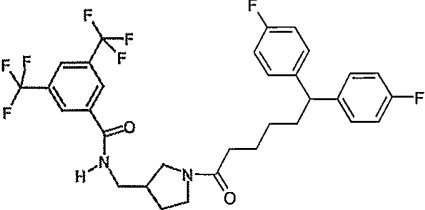
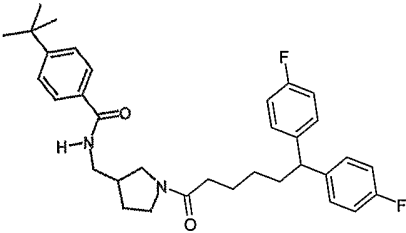
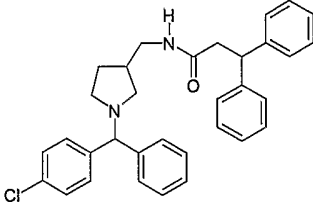
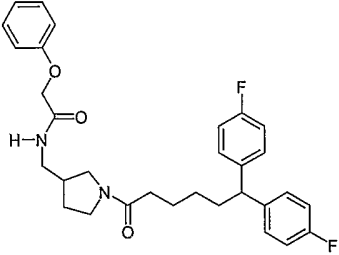
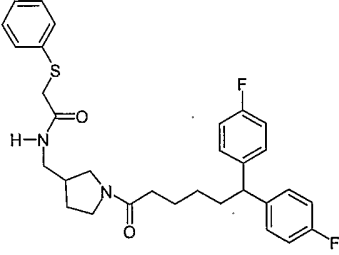
Continuation of Figure 1

#	Name	Structure
P12	[6,6-Bis-(4-fluoro-phenyl)-hexyl]-[1-(3,5-di-tert-butyl-4-methoxy-benzyl)-pyrrolidin-3-ylmethyl]-amine	
P13	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide	
P14	{1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-(3,5-di-tert-butyl-4-methoxy-benzyl)-amine	
P15	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-dibromo-4-hydroxy-benzamide	
P16	4-[(1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl)-amino]-2,6-dibromo-phenol	
P17	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-benzamide	

Continuation of Figure 1

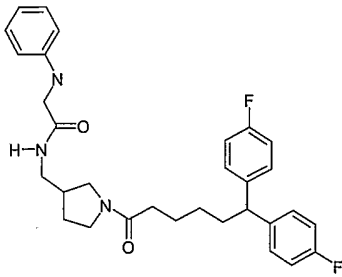
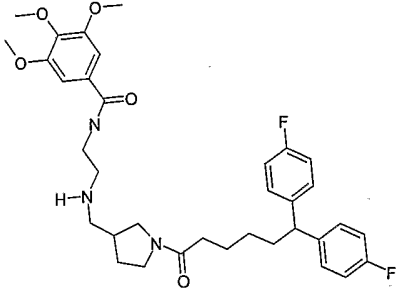
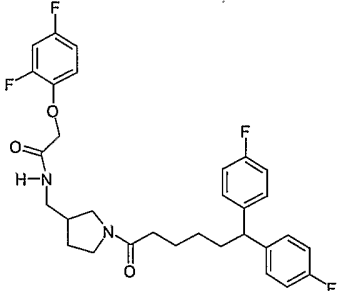
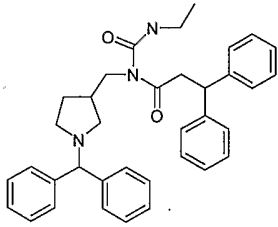
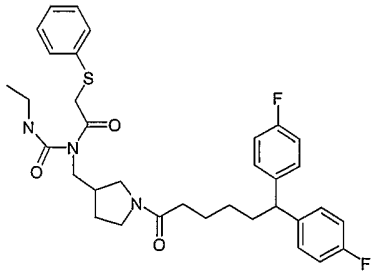
#	Name	Structure
P18	{1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-(3,5-di-tert-butyl-benzyl)-amine	
P19	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide	
P20	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-3,4,5-trimethoxy-benzamide	
P21	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide	
P22	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-(2-dimethylamino-ethoxy)-benzamide	
P23	6,6-Bis-(4-fluoro-phenyl)-hexanoic acid {1-[3,5-di-tert-butyl-4-(2-dimethylamino-ethoxy)-benzoyl]-pyrrolidin-3-ylmethyl}-amide	

Continuation of Figure 1

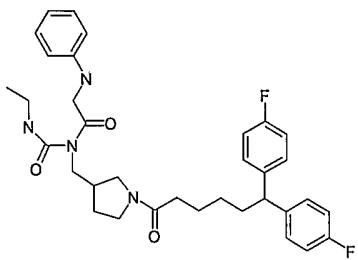
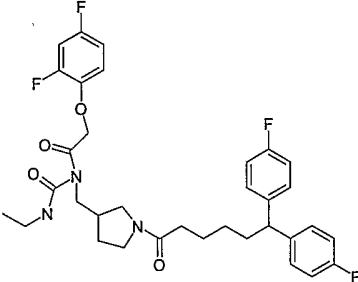
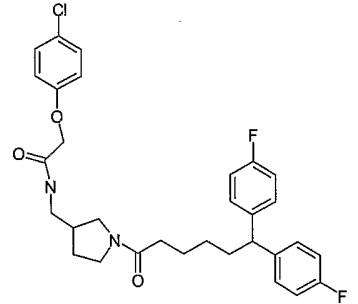
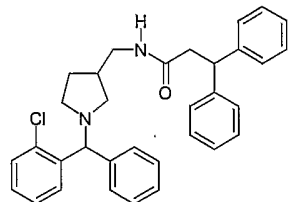
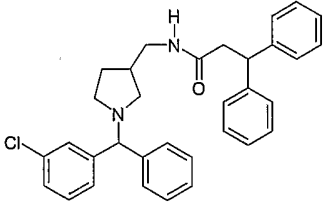
#	Name	Structure
P24	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide	
P25	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-4-tert-butyl-benzamide	
P26	N-{1-[(4-Chloro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-diphenyl-propionamide	
P27	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-phenoxy-acetamide	
P28	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-phenylsulfanyl-acetamide	

Continuation of Figure 1

5/14

#	Name	Structure
P29	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-phenylamino-acetamide	
P30	N-[2-({1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-amino)-ethyl]-3,4,5-trimethoxy-benzamide	
P31	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(2,4-difluoro-phenoxy)-acetamide	
P32	1-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-1-(3,3-diphenyl-propionyl)-3-ethyl-urea	
P33	1-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3-ethyl-1-(2-phenylsulfanyl-acetyl)-urea	

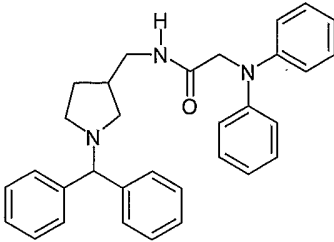
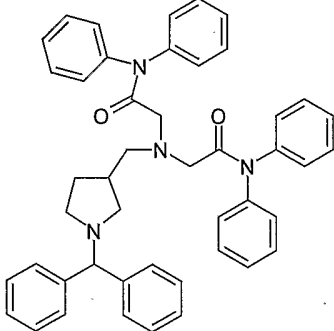
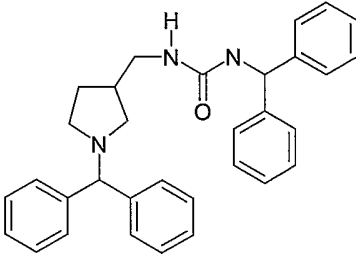
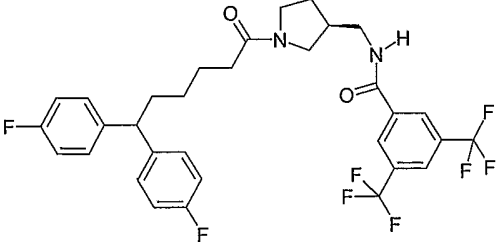
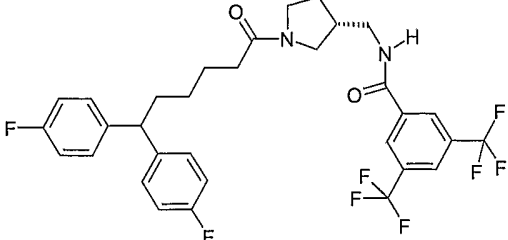
Continuation of Figure 1

#	Name	Structure
P34	1-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3-ethyl-1-(2-phenylamino-acetyl)-urea	
P35	1-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-1-[2-(2,4-difluoro-phenoxy)-acetyl]-3-ethyl-urea	
P36	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(4-chloro-phenoxy)-acetamide	
P37	N-{1-[(2-Chloro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-diphenyl-propionamide	
P38	N-{1-[(3-Chloro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-diphenyl-propionamide	

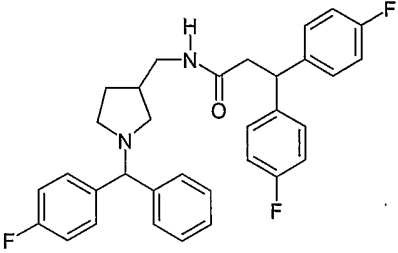
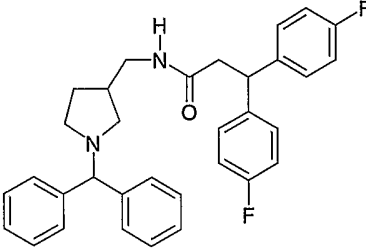
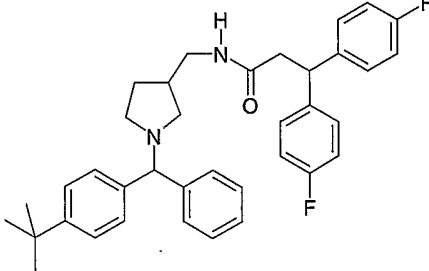
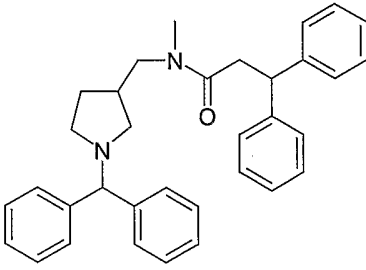
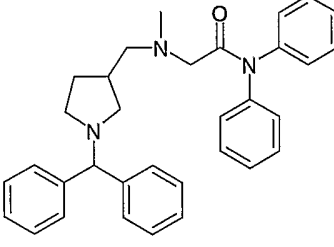
Continuation of Figure 1

#	Name	Structure
P39	3,3-Diphenyl-N-{1-[phenyl-(4-trifluoromethyl-phenyl)-methyl]-pyrrolidin-3-ylmethyl}-propionamide	
P40	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(3,5-dimethyl-phenylamino)-acetamide	
P41	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-2-(3,5-dimethyl-phenylamino)-acetamide	
P42	R-N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide	
P43	S-N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-4-methoxy-benzamide	
P44	R-N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-benzamide	

Continuation of Figure 1

#	Name	Structure
P45	S-N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-di-tert-butyl-benzamide	
P46	N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-2-diphenylamino-acetamide	
P47	2-{(1-Benzhydryl-pyrrolidin-3-ylmethyl)-[(diphenylcarbamoyl)-methyl]-amino}-N,N-diphenyl-acetamide	
P48	1-Benzhydryl-3-(1-benzhydryl-pyrrolidin-3-ylmethyl)-urea	
P49	S-N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide	

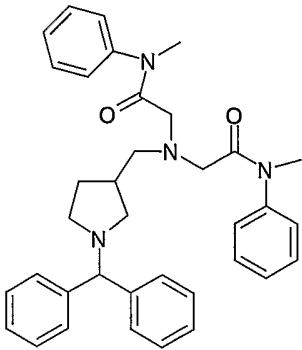
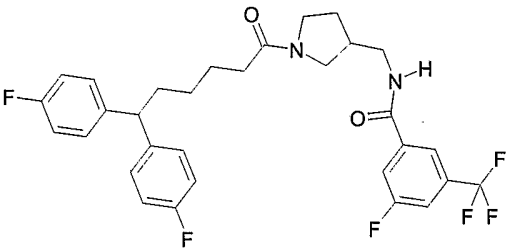
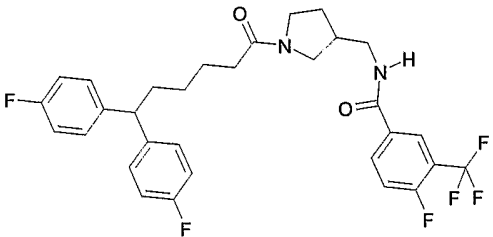
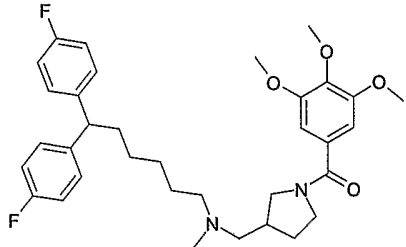
Continuation of Figure 1

#	Name	Structure
P50	R-N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3,5-bis-trifluoromethyl-benzamide	
P51	3,3-Bis-(4-fluoro-phenyl)-N-{1-[(4-fluoro-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-propionamide	
P52	N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-3,3-bis-(4-fluoro-phenyl)-propionamide	
P53	N-{1-[(4-tert-Butyl-phenyl)-phenyl-methyl]-pyrrolidin-3-ylmethyl}-3,3-bis-(4-fluoro-phenyl)-propionamide	
P54	N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-N-methyl-3,3-diphenyl-propionamide	

Continuation of Figure 1

#	Name	Structure
P55	2-[(1-Benzhydryl-pyrrolidin-3-ylmethyl)-methyl-amino]-N,N-diphenyl-acetamide	
P56	N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-N-methyl-N',N'-diphenyl-ethane-1,2-diamine	
P57	(1-Benzhydryl-pyrrolidin-3-ylmethyl)-(3,3-diphenyl-propyl)-methyl-amine	
P58	1-(3-{[(3,5-Bis-trifluoromethyl-benzyl)-methyl-amino]-methyl}-pyrrolidin-1-yl)-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P59	6,6-Bis-(4-fluoro-phenyl)-1-(3-{[methyl-(3,4,5-trimethoxy-benzyl)-amino]-methyl}-pyrrolidin-1-yl)-hexan-1-one	

Continuation of Figure 1

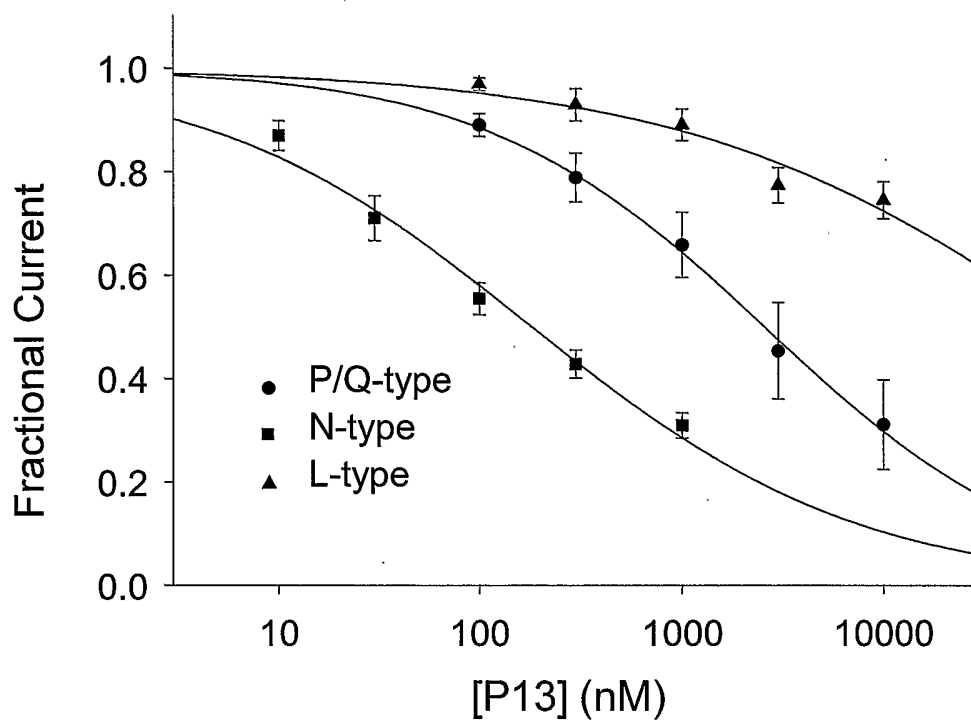
#	Name	Structure
P60	N-(1-Benzhydryl-pyrrolidin-3-ylmethyl)-N-(2-diphenylamino-ethyl)-N',N'-diphenyl-ethane-1,2-diamine	
P61	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-3-fluoro-5-trifluoromethyl-benzamide	
P62	N-{1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-pyrrolidin-3-ylmethyl}-4-fluoro-3-trifluoromethyl-benzamide	
P63	[3-({[6,6-Bis-(4-fluoro-phenyl)-hexyl]-methyl-amino}-methyl)-pyrrolidin-1-yl]-(3,4,5-trimethoxy-phenyl)-methanone	

Continuation of Figure 1

12/14

SUBSTITUTE SHEET (RULE 26)

Effect of P13 on Various Ca^{2+} Channels



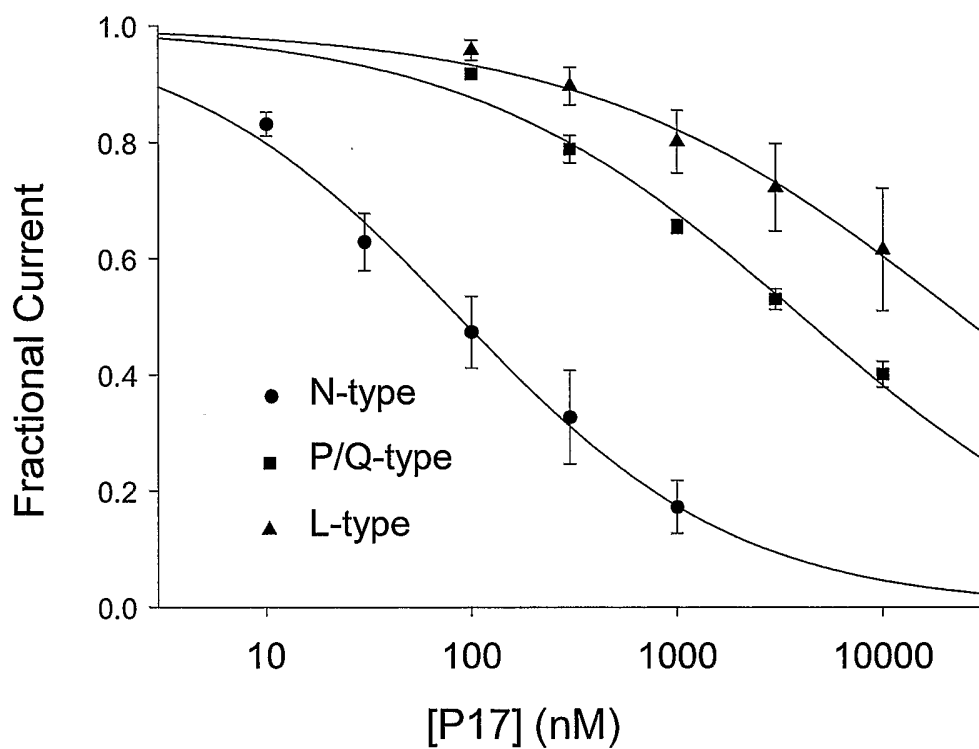
P/Q-type $\text{IC}_{50} = 4225 \pm 1423 \text{ nM}$ ($n=5$)

N-type $\text{IC}_{50} = 198 \pm 43 \text{ nM}$ ($n=5$)

L-type $\text{IC}_{50} \gg 10 \mu\text{M}$ ($n=5$) (estimate: $91 \mu\text{M}$)

Figure 2

Effect of P17 on Various Ca^{2+} Channels



P/Q-type $\text{IC}_{50} = 4116 \pm 327 \text{ nM}$ ($n=5$)

N-type $\text{IC}_{50} = 133 \pm 61 \text{ nM}$ ($n=6$)

L-type $\text{IC}_{50} > 10 \mu\text{M}$ ($n=5$) (estimate :13.2 μM)

Figure 3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA2004/000797

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/40 C07D207/09 A61P9/00 A61P25/00

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 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92/22527 A (SMITHKLINE BEECHAM PLC) 23 December 1992 (1992-12-23) page 3, line 9 - line 23; claim 1; examples 14,15	1-29
A	COX B; DENYER J C: "N-type calcium channel blockers in pain and stroke" EXPERT OPINION ON THERAPEUTIC PATENTS., vol. 8, no. 10, 1998, pages 1237-1250, XP002292472 GBASHLEY PUBLICATIONS. section 3 ----- -/--	1-29

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 document 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

16 August 2004

Date of mailing of the international search report

30/08/2004

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Authorized officer

Seymour, L

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA2004/000797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VALENTA V ET AL.: "Potential nootropic agents: Synthesis of some 1,4-disubstituted 2-oxopyrrolidines and some related compounds" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 59, no. 5, 1994, pages 1126-1136, XP009035253 GBACADEMIC PRESS, LONDON. compounds IVb - IVd page 1129, line 16 - line 26 -----	1-29
X	WO 03/029199 A (YAMAMOTO MASATAKA ; MATSUMOTO TAKAHIRO (JP); MOCHIZUKI MANABU (JP); NA) 10 April 2003 (2003-04-10) abstract page 253, line 5 page 259, line 10 -----	1-29
X	WO 99/09984 A (LYNCH CHRISTOPHER ; HOLSON EDWARD (US); BERK SCOTT C (US); BUDHU RICHA) 4 March 1999 (1999-03-04) examples 15,19 -----	1-23
X	WO 97/27180 A (VERTEX PHARMA ; TUNG ROGER DENNIS (US); SALITURO FRANCESCO GERALD (US)) 31 July 1997 (1997-07-31) example 95 -----	1-23
X	EP 0 640 601 A (HOKURIKU PHARMACEUTICAL) 1 March 1995 (1995-03-01) page 8, line 15 page 15, line 28 -----	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/000797

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24 and 26–29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims 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. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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 an additional fee, this Authority did not invite payment of any additional fee.
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 claims 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 claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA2004/000797

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9222527	A	23-12-1992	AU 1975092 A EP 0589971 A1 WO 9222527 A2 JP 6508353 T	12-01-1993 06-04-1994 23-12-1992 22-09-1994
WO 03029199	A	10-04-2003	EP 1437344 A1 WO 03029199 A1	14-07-2004 10-04-2003
WO 9909984	A	04-03-1999	AU 9206798 A CA 2298813 A1 EP 1009405 A1 JP 2001526178 T WO 9909984 A1 US 6166037 A	16-03-1999 04-03-1999 21-06-2000 18-12-2001 04-03-1999 26-12-2000
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EP 0640601	A	01-03-1995	CA 2103590 A1 DE 69215694 D1 DE 69215694 T2 EP 0640601 A1 US 5395832 A US 5500422 A AT 145906 T DK 640601 T3 ES 2096073 T3 JP 3104142 B2 JP 5262724 A WO 9214705 A1 KR 159961 B1	16-08-1992 16-01-1997 28-05-1997 01-03-1995 07-03-1995 19-03-1996 15-12-1996 02-06-1997 01-03-1997 30-10-2000 12-10-1993 03-09-1992 01-12-1998