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(54) **CALCIUM RECEPTOR-ACTIVE COMPOUNDS**

KALZIUM-REZEPTOR AKTIVE VERBINDUNGEN

COMPOSES CAPABLES DE MODULER L'ACTIVITE DU RECEPTEUR DE CALCIUM

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(73) Proprietor: **NPS PHARMACEUTICALS, INC.**
Salt Lake City, UT 84108 (US)

(72) Inventors:
- **VAN WAGENEN, Bradford, C.**
Salt Lake City, UT 84124 (US)
- **MOE, Scott, T.**
Salt Lake City, UT 84121 (US)
- **BALANDRIN, Manuel, F.**
Sandy, UT 84093 (US)
- **DELMAR, Eric, G.**
Salt Lake City, UT 84108 (US)
- **NEMETH, Edward, F.**
Salt Lake City, UT 84124 (US)

(74) Representative: **Jaenichen, Hans-Rainer et al**
Vossius & Partner,
Postfach 86 07 67
81634 München (DE)

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

Field of the Invention

[0001] This invention relates to the use of compounds able to modulate one or more inorganic ion receptor activities.

Background of the Invention

[0002] Certain cells in the body respond not only to chemical signals, but also to ions such as extracellular calcium ions (Ca^{2+}). Changes in the concentration of extracellular Ca^{2+} (referred to herein as "[Ca^{2+}]") alter the functional responses of these cells. One such specialized cell is the parathyroid cell which secretes parathyroid hormone (PTH). PTH is the principal endocrine factor regulating Ca^{2+} homeostasis in the blood and extracellular fluids.

[0003] PTH, by acting on bone and kidney cells, increases the level of Ca^{2+} in the blood. This increase in [Ca^{2+}] then acts as a negative feedback signal, depressing PTH secretion. The reciprocal relationship between [Ca^{2+}] and PTH secretion forms the essential mechanism maintaining bodily Ca^{2+} homeostasis.

[0004] Extracellular Ca^{2+} acts directly on parathyroid cells to regulate PTH secretion. The existence of a parathyroid cell surface protein which detects changes in [Ca^{2+}] has been confirmed. Brown et al., 366 Nature 574, 1993. In parathyroid cells, this protein acts as a receptor for extracellular Ca^{2+} ("the calcium receptor"), and detects changes in [Ca^{2+}] and to initiate a functional cellular response, PTH secretion.

[0005] Extracellular Ca^{2+} can exert effects on different cell functions, reviewed in Nemeth et al., 11 Cell Calcium 319, 1990. The role of extracellular Ca^{2+} in parafollicular (C-cells) and parathyroid cells is discussed in Nemeth, 11 Cell Calcium 323, 1990. These cells have been shown to express similar Ca^{2+} receptor. Brown et al., 366 Nature 574, 1993; Mithal et al., 9 Suppl. 1 J. Bone and Mineral Res. s282, 1994; Rogers et al., 9 Suppl. 1 J. Bone and Mineral Res. s409, 1994; Garrett et al., 9 Suppl. 1 J. Bone and Mineral Res. s409, 1994. The role of extracellular Ca^{2+} on bone osteoclasts is discussed by Zaidi, 10 Bioscience Reports 493, 1990. In addition keratinocytes, juxtaglomerular cells, trophoblasts, pancreatic beta cells and fat/adipose cells all respond to increases in extracellular calcium which likely reflects activation of calcium receptors of these cells.

[0006] The ability of various compounds to mimic extracellular Ca^{2+} *in vitro* is discussed by Nemeth et al., (spermine and spermidine) in "Calcium-Binding Proteins in Health and Disease," 1987, Academic Press, Inc., pp. 33-35; Brown et al., (e.g., neomycin) 128 Endocrinology 3047, 1991; Chen et al., (diltiazem and its analog, TA-3090) 5 J. Bone and Mineral Res. 581, 1990; and Zaidi et al., (verapamil) 167 Biochem. Biophys. Res. Commun. 807, 1990. Nemeth *et al.*, PCT/US93/01642, International Publication Number WO 94/18959, and Nemeth *et al.*, PCT/US92/07175, International Publication Number WO 93/04373, describe various compounds which can modulate the effect of an inorganic ion on a cell having an inorganic ion receptor.

[0007] The references provided in the background are not admitted to be prior art.

Summary of the Invention

[0008] The present invention features compounds able to modulate one or more activities of an inorganic ion receptor and methods for treating diseases or disorders by modulating inorganic ion receptor activity. Preferred compounds can mimic or block the effect of extracellular calcium on a cell surface calcium receptor.

[0009] Diseases or disorders which can be treated by modulating inorganic ion receptor activity include one or more of the following types: (1) those characterized by abnormal inorganic ion homeostasis, preferably calcium homeostasis; (2) those characterized by an abnormal amount of an extracellular or intracellular messenger whose production can be affected by inorganic ion receptor activity, preferably calcium receptor activity; (3) those characterized by an abnormal effect (*e.g.,* a different effect in kind or magnitude) of an intracellular or extracellular messenger which can itself be ameliorated by inorganic ion receptor activity, preferably calcium receptor activity; and (4) other diseases or disorders in which modulation of inorganic ion receptor activity, preferably calcium receptor activity will exert a beneficial effect, for example, in diseases or disorders where the production of an intracellular or extracellular messenger stimulated by receptor activity compensates for an abnormal amount of a different messenger. Examples of extracellular messengers whose secretion and/or effect can be affected by modulating inorganic ion receptor activity include inorganic ions, hormones, neurotransmitters, growth factors, and chemokines. Examples of intracellular messengers include cAMP, cGMP, IP_3, and diacylglycerol.

[0010] Thus, a compound of this invention preferably modulates calcium receptor activity and is used in the treatment of diseases or disorders which can be affected by modulating one or more activities of a calcium receptor. Calcium receptor proteins enable certain specialized cells to respond to changes in extracellular Ca^{2+} concentration. For example, extracellular Ca^{2+} inhibits the secretion of parathyroid hormone from parathyroid cells, inhibits bone resorption by osteoclasts, and stimulates secretion of calcitonin from C-cells.

[0011] In a preferred embodiment, the compound is used to treat a disease or disorder characterized by abnormal bone and mineral homeostasis, more preferably calcium homeostasis. Extracellular Ca^{2+} is under tight homeostatic control and controls various processes such as blood clotting, nerve and muscle excitability, and proper bone formation. Abnormal calcium homeostasis is characterized by one or more of the following activities: (1) an abnormal increase or decrease in serum calcium; (2) an abnormal increase or decrease in urinary excretion of calcium; (3) an abnormal increase or decrease in bone calcium levels, for example, as assessed by bone mineral density measurements; (4) an abnormal absorption of dietary calcium; (5) an abnormal increase or decrease in the production and/or release of messengers which affect serum calcium levels such as parathyroid hormone and calcitonin; and (6) an abnormal change in the response elicited by messengers which affect serum calcium levels. The abnormal increase or decrease in these different aspects of calcium homeostasis is relative to that occurring in the general population and is generally associated with a disease or disorder.

[0012] Diseases and disorders characterized by abnormal calcium homeostasis can be due to different cellular defects such as a defective calcium receptor activity, a defective number of calcium receptors, or a defective intracellular protein acted on by a calcium receptor. For example, in parathyroid cells, the calcium receptor is coupled to the G_i protein which in turn inhibits cyclic AMP production. Defects in G_i protein can affect its ability to inhibit cyclic AMP production. Inorganic ion receptor-modulating compound include ionomimetics, ionolytics, calcimimetics, and calcilytics. Ionomimetics are compounds which bind to an inorganic ion receptor and mimic (*i.e.*, evoke or potentiate) the effects of an inorganic ion at an inorganic ion receptor. Preferably, the compound affects one or more calcium receptor activities. Calcimimetics are ionomimetics which effects one or more calcium receptor activities and bind to a calcium receptor.

[0013] Ionolytics are compounds which bind to an inorganic ion receptor and block (*i.e.*, inhibit or diminish) one or more activities caused by an inorganic ion at an inorganic ion receptor. Preferably, the compound affects one or more calcium receptor activities. Calcilytics are ionolytics which block one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.

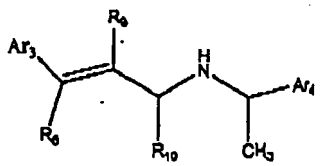
[0014] Ionomimetics and ionolytics may bind at the same receptor site as the native inorganic ion ligand binds or can bind at a different site (*e.g.*, allosteric site). For example, NPS *R*-467 binding to a calcium receptor results in calcium receptor activity and, thus, NPS *R*-467 is classified as a calcimimetic. However, NPS *R*-467 binds to the calcium receptor at a different site (*i.e.*, an allosteric site) than extracellular calcium.

[0015] A measure of a compounds effectiveness can be determined by calculating the EC_{50} or IC_{50} for that compound. The EC_{50} is the concentration of a compound which causes a half maximal mimicking effect. The IC_{50} is the concentration of compound which causes a half-maximal blocking effect. EC_{50} and IC_{50} for compounds at a calcium receptor can be determined by assaying one or more of the activities of extracellular calcium at a calcium receptor. Examples of assays for measuring EC_{50}, and IC_{50} are described Nemeth et *al.*, PCT/US93/01642, International Publication Number WO 94/18959, WO 95/11221 and Nemeth *et al.*, PCT/US92/07175, International Publication Number WO 93/04373, and below. Such assays include oocyte expression assays and measuring increases in intracellular calcium ion concentration ($[Ca^{2+}]_i$) due to calcium receptor activity. Preferably, such assays measure the release or inhibition of a particular hormone associated with activity of a calcium receptor.

[0016] An inorganic ion receptor-modulating compound preferably selectively targets inorganic ion receptor activity in a particular cell. For example, selective targeting of a calcium receptor activity is achieved by a compound exerting a greater effect on a calcium receptor activity in one cell type than at another cell type for a given concentration of compound. Preferably, the differential effect is 10-fold or greater as measured *in vivo* or *in vitro*. More preferably, the differential effect is measured *in vivo* and the compound concentration is measured as the plasma concentration or extracellular fluid concentration and the measured effect is the production of extracellular messengers such as plasma calcitonin, parathyroid hormone, or plasma calcium. For example, in a preferred embodiment, the compound selectively targets PTH secretion over calcitonin secretion.

[0017] Preferably, the compound is either a calcimimetic or calcilytic having an EC_{50} or IC_{50} at a calcium receptor of less than or equal to 5 μM, and even more preferably less than or equal to 1 μM, 100 nmolar, 10 nmolar, or 1 nmolar using one of the assays described below. More preferably, the assay measures intracellular Ca^{2+} in HEK 293 cells transformed with nucleic acid expressing the human parathyroid calcium receptor and loaded with fura-2. Lower EC_{50}'s or IC_{50}'s are advantageous since they allow lower concentrations of compounds to be used *in vivo* or *in vitro*. The discovery of compounds with low EC_{50}'s and IC_{50}'s enables the design and synthesis of additional compounds having similar or improved potency, effectiveness, and/or selectivity.

[0018] A first aspect the present invention features an inorganic ion receptor modulating compound having the formula:



wherein Ar_3 is phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of: C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, benzyl, benzyloxy, dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acetyl, and ethylene dioxy; independently selected from the group consisting of C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, and acetoxy;
R_8 is either hydrogen or phenyl;
R_9 is either hydrogen or methyl; and
R_{10} is either hydrogen, methyl, or phenyl;
or a pharmaceutically acceptable salt or complex thereof.

[0019] Another aspect of the present invention features a pharmaceutical composition made up of an inorganic ion receptor-modulating compound described herein and a physiologically acceptable carrier. A "pharmacological composition" refers to a composition in a form suitable for administration into a mammal, preferably a human. Preferably, the pharmaceutical composition contains a sufficient amount of a calcium receptor modulating compound in a proper pharmaceutical form to exert a therapeutic effect on a human.

[0020] Considerations concerning forms suitable for administration are known in the art and include toxic effects, solubility, route of administration, and maintaining activity. For example, pharmacological compositions injected into the blood stream should be soluble.

[0021] Pharmaceutical compositions can also be formulated as pharmaceutically acceptable salts (*e.g.*, acid addition salts) and complexes thereof. The preparation of such salts can facilitate the pharmacological use of a compound by altering its physical characteristics without preventing it from exerting a physiological effect.

[0022] Another aspect the present invention features a method for treating a patient by modulating inorganic ion receptor activity using inorganic ion receptor modulating compounds described herein. The method involves administering to the patient a pharmaceutical composition containing a therapeutically effective amount of an inorganic ion receptor-modulating compound. In a preferred embodiment, the disease or disorder is treated by modulating calcium receptor activity by administering to the patient a therapeutically effective amount of a calcium receptor-modulating compound.

[0023] Inorganic ion receptor-modulating compounds, and compositions containing the compounds, can be used to treat patients. A "patient" refers to a mammal in which modulation of an inorganic ion receptor will have a beneficial effect. Patients in need of treatment involving modulation of inorganic ion receptors can be identified using standard techniques known to those in the medical profession.

[0024] Preferably, a patient is a human having a disease or disorder characterized by one more of the following: (1) abnormal inorganic ion homeostasis, more preferably abnormal calcium homeostasis; (2) an abnormal level of a messenger whose production or secretion is affected by inorganic ion receptor activity, more preferably affected by calcium receptor activity; and (3) an abnormal level or activity of a messenger whose function is affected by inorganic ion receptor activity, more preferably affected by calcium receptor activity.

[0025] Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, osteoporosis and other bone and mineral-related disorders, and the like (as described, *e.g.*, in standard medical text books, such as "Harrison's Principles of Internal Medicine"). Such diseases are treated using calcium receptor-modulating compounds which mimic or block one or more of the effects of extracellular $Ca2^+$ on a calcium receptor and, thereby, directly or indirectly affect the levels of proteins or other compounds in the body of the patient.

[0026] By "therapeutically effective amount" is meant an amount of a compound which relieves to some extent one or more symptoms of the disease or disorder in the patient; or returns to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of the disease or disorder.

[0027] In a preferred embodiment, the patient has a disease or disorder characterized by an abnormal level of one or more calcium receptor-regulated components and the compound is active on a calcium receptor of a cell selected from the group consisting of: parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell, GI tract cell, skin cell, adrenal cell, pituitary cell, hypothalamic cell and cell of the subfornical organ.

[0028] More preferably, the cells are chosen from the group consisting of: parathyroid cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct in the kidney, parafollicular cell in the thyroid (C-cell), intestinal cell, GI tract cell, pituitary cell, hypothalamic cell and cell of the subfornical organ.

[0029] In a preferred embodiment, the compound is a calcimimetic acting on a parathyroid cell calcium receptor and reduces the level of parathyroid hormone in the serum of the patient. More preferably, the level is reduced to a degree sufficient to cause a decrease in plasma Ca^{2+}. Most preferably, the parathyroid hormone level is reduced to that present in a normal individual.

[0030] In another preferred embodiment, the compound is a calcilytic acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient. More preferably, the level is increased to a degree sufficient to cause an increase in bone mineral density of a patient.

[0031] Patients in need of such treatments can be identified by standard medical techniques, such as blood or urine analysis. For example, by detecting a deficiency of protein whose production or secretion is affected by changes in inorganic ion concentrations, or by detecting abnormal levels of inorganic ions or hormones which effect inorganic ion homeostasis.

[0032] Various examples are used throughout the application. These examples are not intended in any way to limit the invention.

[0033] Other features and advantages of the invention will be apparent from the following figures, detailed description of the invention, examples, and the claims.

Brief Description of the Drawings

[0034]

Figs. 1f-1h, show the chemical structures of different compounds.
Figs. 30-35 and 91-94 provided physical data for representative compounds herein described.

Description of the Preferred Embodiments

[0035] The present invention features compounds able to modulate one or more inorganic ion receptor activities, preferably the compound can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor. Publications concerned with the calcium activity, calcium receptor and/or calcium receptor modulating-compounds include the following: Brown et al., Nature 366: 574, 1993; Nemeth *et al.*, PCT/US93/01642, International Publication Number WO 94/18959; Nemeth *et al.*, PCT/US92/07175, International Publication Number WO 93/04373; Shoback and Chen, J. Bone Mineral Res. 9: 293 (1994); and Racke et al., FEBS Lett. 333: 132, (1993). These publications are not admitted to be prior art to the claimed invention.

I. Calcium Receptors

[0036] Calcium receptors are present on different cell types and can have different activities in different cell types. The pharmacological effects of the following cells, in response to calcium, is consistent with the presence of a calcium receptor: parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or, collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell, GI tract cell, skin cell, adrenal cell, pituitary cell, hypothalamic cell and-cell of the subfornical organ. In addition, the presence of calcium receptors on parathyroid cell, central nervous system cell, peripheral nervous, system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct in the kidney, parafollicular cell in the thyroid (C-cell), intestinal cell, GI tract cell, pituitary cell, hypothalamic cell and.cell of the subfornical organ, has been confirmed by physical data.

[0037] The calcium receptor on these different cell types may be different. It is also possible that a cell can have more than one type of calcium receptor. Comparison of calcium receptor activities and amino acid sequences from different cells indicate that distinct calcium receptor types exist. For example, calcium receptors can respond to a variety of di- and trivalent cations. The parathyroid calcium receptor responds to calcium and Gd^{3+}, while osteoclasts respond to divalent cations such as calcium, but do not respond to Gd^{3+}. Thus, the parathyroid calcium receptor is pharmacologically distinct from the calcium receptor on the osteoclast.

[0038] On the other hand, the nucleic acid sequences encoding calcium receptors present in parathyroid cells and C-

cells indicate that these receptors have a very similar amino acid structure. Nevertheless, calcimimetic compounds exhibit differential pharmacology and regulate different activities at parathyroid cells and C-cells. Thus, pharmacological properties of calcium receptors may vary, significantly depending upon the cell type or organ in which they are expressed even though the calcium receptors may have similar or even identical structures.

[0039] Calcium receptors, in general, have a low affinity for extracellular Ca^{2+} (apparent K_d generally greater than about 0.5 mM). Calcium receptors may include a free or bound effector mechanism as defined by Cooper, Bloom and Roth, "The Biochemical Basis of Neuropharmacology", Ch. 4, and are thus distinct from intracellular calcium receptors, *e.g.*, calmodulin and the troponins.

[0040] Calcium receptors respond to changes in extracellular calcium levels. The exact changes depend on the particular receptor and cell line containing the receptor. For example, the *in vitro* effect of calcium on the calcium receptor in a parathyroid cell includes the following:

1. An increase in internal calcium. The increase is due to the influx of external calcium and/or to mobilization of internal calcium. Characteristics of the increase in internal calcium include the following:

   (a) A rapid (time to peak < 5 seconds) and transient increase in $[Ca^{2+}]_i$ that is refractory to inhibition by 1 μM La^{3+} or 1 μM Gd^{3+} and is abolished by pretreatment with ionomycin (in the absence of extracellular Ca^{2+}) ;
   (b) The increase is not inhibited by dihydropyridines;
   (c) The transient increase is abolished by pretreatment for 10 minutes with 10 mM sodium fluoride;
   (d) The transient increase is diminished by pretreatment with an activator of protein kinase C (PKC), such as phorbol myristate acetate (PMA), mezerein or (-)-indolactam V. The overall effect of the protein kinase C activator is to shift the concentration-response curve of calcium to the right without affecting the maximal response; and
   (e) Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect the increase.

2. A rapid (< 30 seconds) increase in the formation of inositol-1,4,5-triphosphate or diacylglycerol. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect this increase;
3. The inhibition of dopamine- and isoproterenol-stimulated cyclic AMP formation. This effect is blocked by pretreatment with pertussis toxin (100 ng/ml for > 4 hours); and
4. The inhibition of PTH secretion. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect the inhibition in PTH secretion.

[0041] Using techniques known in the art, the effect of calcium on other calcium receptors in different cells can be readily determined. Such effects may be similar in regard to the increase in internal calcium observed in parathyroid cells. However, the effect is expected to differ in other aspects, such as causing or inhibiting the release of a hormone other than parathyroid hormone.

II. Inorganic Ion Receptor Modulating Compounds

[0042] Inorganic ion receptor modulating compounds modulate one or more inorganic ion receptor activities. Preferred calcium receptor modulating compounds are calcimimetics and calcilytics. Inorganic ion receptor modulating compounds can be identified by screening compounds which are modelled after a compound shown to have a particular activity (*i.e.*, a lead compound).

[0043] A preferred method of measuring calcium receptor activity is to measure changes in $[Ca^{2+}]_i$. Changes in $[Ca^{2+}]_i$ can be measured using different techniques such by using HEK 293 cells transduced with nucleic acid expressing the human parathyroid calcium receptor and loaded with fura-2; and by measuring an increase in Cl^- current in a *Xenopus* oocyte injected with nucleic acid coding for a calcium receptor. (See Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.) For example, poly(A)$^+$ mRNA can be obtained from cells expressing a calcium receptor, such as a parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, central nervous cell, peripheral nervous system cell, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell, and GI tract cell. Preferably, the nucleic acid is from a parathyroid cell, C-cell, or osteoclast. More preferably, the nucleic acid encodes a calcium receptor and is present on a plasmid or vector.

[0044] In preferred embodiments the calcium receptor modulating compound is a calcimimetic which inhibits bone resorption *in vivo* by an osteoclast; inhibits bone resorption *in vitro* by an osteoclast; stimulates calcitonin secretion *in vitro* or *in vivo* from a c-cell; inhibits parathyroid hormone secretion from a parathyroid cell *in vitro* and decreases PTH secretion *in vivo*; elevates calcitonin levels *in vivo*; or blocks osteoclastic bone resorption *in vitro* and inhibits bone

resorption *in vivo*.

[0045] In another preferred embodiment the calcium receptor modulating compound is a calcilytic which evokes the secretion of parathyroid hormone from parathyroid cells *in vitro* and elevates the level of parathyroid hormone *in vivo.*

[0046] Preferably, the compound selectively targets inorganic ion receptor activity, more preferably calcium receptor activity, in a particular cell. By "selectively" is meant that the compound exerts a greater effect on inorganic ion receptor activity in one cell type than at another cell type for a given concentration of compound. Preferably, the differential effect is 10-fold or greater. Preferably, the concentration refers to blood plasma concentration and the measured effect is the production of extracellular messengers such as plasma calcitonin, parathyroid hormone or plasma calcium. For example, in a preferred embodiment, the compound selectively targets PTH secretion over calcitonin secretion.

[0047] In another preferred embodiment, the compound has an EC_{50} or IC_{50} less than or equal to 5 μM at one or more, but not all cells chosen from the group consisting of: parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell, GI tract cell, skin cell, adrenal cell, pituitary cell, hypothalamic cell and cell of the subfornical organ. More preferably, the cells are chosen from the group consisting of parathyroid cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct in the kidney, parafollicular cell in the thyroid (C-cell), intestinal cell, GI tract cell, pituitary cell, hypothalamic cell and cell of the subfornical organ. The presence of a calcium receptor in this group of cells has been confirmed by physical data such as in situ hybridization and antibody staining.

[0048] Preferably, inorganic ion receptor modulating compounds mimic or block the effects of an extracellular ion on a cell having an inorganic ion receptor, such that the compounds achieve a therapeutic effect. Inorganic ion receptor modulating compounds may have the same, or different, effects on cells having different types of inorganic ion receptor morphology (*e.g.,* such as cells having normal inorganic ion receptors, a normal number of inorganic ion receptor, an abnormal inorganic ion receptor, and an abnormal number of inorganic ion receptors).

[0049] Calcium receptor modulating compounds preferably mimic or block all of the effects of extracellular ion in a cell having a calcium receptor. However, calcimimetics need not possess all the biological activities of extracellular Ca^{2+}. Similarly, calcilytics need not block all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different calcilytics do not need to bind to the same site on the calcium receptor as does extracellular Ca^{2+} to exert their effects.

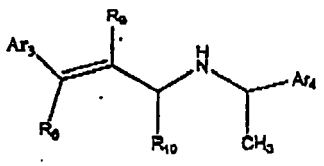
[0050] Inorganic modulating compounds need not effect inorganic receptor activity to the same extent or in exactly the same manner as the natural ligand. For example, a calcimimetic may effect calcium receptor activity to a different extent, to a different duration, by binding to a different binding site, or by having a different affinity, compared to calcium acting at a calcium receptor.

A. Calcimimetics

Structure I Compounds

2. Structure II Compounds

[0051] Structure II compounds have the formula:



wherein A-r_3 is phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of: C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, benzyl, benzyloxy, dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acetyl, and ethylene dioxy; independently selected from the group consisting of C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, and acetoxy;

R_8 is either hydrogen or phenyl;

R_9 is either hydrogen or methyl; and

R_{10} is either hydrogen, methyl, or phenyl;
or a pharmaceutically acceptable salt or complex thereof.

[0052] More preferably when R_{10} is methyl the chiral carbon it is attached to is the (*R*) stereoisomer.

[0053] Preferably, the α-methyl in Structure II is an (*R*)-α-methyl.

3. Calcimimetic Activity

[0054] The ability of compounds to mimic the activity of Ca^{2+} at calcium receptors can be determined using procedures known in the art and described by Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959. For example, calcimimetics possess one or more and preferably all of the following activities when tested on parathyroid cells *in vitro*:

1. The compound causes a rapid (time to peak < 5 seconds) and transient increase in intracellular calcium concentration that is refractory to inhibition by 1 μM La^{3+} or 1 μM Gd^{3+}. The increase in $[Ca^{2+}]_i$ persists in the absence of extracellular Ca^{2+}, but is abolished by pretreatment with ionomycin (in the absence of extracellular Ca^{2+});
2. The compound potentiates increases in $[Ca^{2+}]_i$ elicited by submaximal concentrations of extracellular Ca^{2+};
3. The increase in $[Ca^{2+}]_i$ elicited by extracellular Ca^{2+} is not inhibited by dihydropyridines;
4. The transient increase in $[Ca^{2+}]_i$ caused by the compound is abolished by pretreatment for 10 minutes with 10 mM sodium fluoride;
5. The transient increase in $[Ca^{2+}]_i$ caused by the compound is diminished by pretreatment with an activator of protein kinase C (PKC), such as phorbol myristate acetate (PMA), mezerein or (-)-indolactam V. The overall effect of the protein kinase C activator is to shift the concentration-response curve of the compound to the right without affecting the maximal response;
6. The compound causes a rapid (< 30 seconds) increase in the formation of inositol-1,4,5-triphosphate and/or diacylglycerol;
7. The compound inhibits dopamine- or isoproterenol-stimulated cyclic AMP formation;
8. The compound inhibits PTH secretion;
9. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) blocks the inhibitory effect of the compound on cyclic AMP formation, but does not effect increases in $[Ca^{2+}]_i$, inositol-1,4,5-triphosphate, or diacylglycerol, nor decreases in PTH secretion;
10. The compound elicits increases in Cl^- current in *Xenopus* oocytes injected with poly $(A)^+$-enriched mRNA from bovine or human parathyroid cells, but is without effect in *Xenopus* oocytes injected with water, or liver mRNA; and
11. Similarly, using a cloned calcium receptor from a parathyroid cell, the compound will elicit a response in *Xenopus* oocytes injected with the specific cDNA or mRNA encoding the receptor.

[0055] Different calcium activities can be measured using available techniques. (*See,* Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.) Parallel definitions of compounds mimicking Ca^{2+} activity on other calcium responsive cell, preferably at a calcium receptor, are evident from the examples provided herein and Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.

[0056] Preferably, the compound as measured by the bioassays described herein, or by Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959, has one or more, more preferably all of the following activities: evokes a transient increase in internal calcium, having a duration of less that 30 seconds (preferably by mobilizing internal calcium); evokes a rapid increase in $[Ca^{2+}]_i$, occurring within thirty seconds; evokes a sustained increase (greater than thirty seconds) in $[Ca^{2+}]_i$ (preferably by causing an influx of external calcium); evokes an increase in inositol-1,4,5-triphosphate or diacylglycerol levels, preferably within less than 60 seconds; and inhibits dopamine- or isoproterenol-stimulated cyclic AMP formation.

[0057] The transient increase in $[Ca^{2+}]_i$ is preferably abolished by pretreatment of the cell for ten minutes with 10 mM sodium fluoride, or the transient increase is diminished by brief pretreatment (not more than ten minutes) of the cell with an activator of protein kinase C, preferably, phorbol myristate acetate (PMA), mezerein or (-) indolactam V.

C. Calcilytics

[0058] The ability of a compound to block the activity of extracellular calcium at a calcium receptor can be determined using standard techniques based on the present disclosure. (See, also Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.) For example, compounds which block the effect of extracellular calcium, when used in reference to a parathyroid cell, possess one or more, and preferably all of the following characteristics when tested on parathyroid cells *in vitro:*

1. The compound blocks, either partially or completely, the ability of increased concentrations of extracellular Ca^{2+} to:

(a) increase $[Ca^{2+}]_i$,
(b) mobilize intracellular Ca^{2+},
(c) increase the formation of inositol-1,4,5-triphosphate,
(d) decrease dopamine- or isoproterenol-stimulated cyclic AMP formation, and
(e) inhibit PTH secretion;

2. The compound blocks increases in Cl^- current in *Xenopus* oocytes injected with poly(A)$^+$-mRNA from bovine or human parathyroid cells elicited by extracellular Ca^{2+} or calcimimetic compounds, but not in *Xenopus* oocytes injected with water or liver mRNA;
3. Similarly, using a cloned calcium receptor from a parathyroid cell, the compound will block a response in *Xenopus* oocytes injected with the specific cDNA, mRNA or cRNA encoding the calcium receptor, elicited by extracellular Ca^{2+} or a calcimimetic compound.

[0059] Parallel definitions of compounds blocking Ca^{2+} activity on a calcium responsive cell, preferably at a calcium receptor, are evident from the examples provided herein and Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.

III. TREATMENT OF DISEASES OR DISORDERS

[0060] Diseases or disorders which can be treated by modulating calcium receptor activity are known in the art. For example, diseases or disorders which can be treated by modulating calcium receptor activity can be identified based on the functional responses of cells regulated by calcium receptor activity. Functional responses of cells regulated by calcium receptor are know in the art, including PTH secretion by parathyroid cells, calcitonin secretion by C-cells, and bone resorption by osteoclasts.

[0061] Such functional responses are associated with different diseases or disorders. For example, hyperparathyroidism results in elevated levels of PTH. in the plasma. Decreasing the plasma levels of PTH offers an effective means of treating hyperparathyroidism. Likewise, increasing plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for osteoporosis. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and osteoporosis.

[0062] Those compounds modulating inorganic ion receptor activity, preferably calcium receptor activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, osteoporosis is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used to block osteoclastic bone resorption either directly (*e.g.*, an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (*e.g.*, a C-cell calcimimetic). Alternatively, a calcilytic active on the parathyroid cell calcium receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from osteoporosis.

[0063] In addition, it is known that intermittent low dosing with PTH results in an anabolic effect on bone mass and appropriate bone remodeling. Thus, compounds and dosing regimens evoking transient increases in parathyroid hormone (*e.g.*, intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from osteoporosis.

[0064] Additional diseases or disorders can be identified by identifying additional cellular functional responses, associated with a disease or disorder, which are regulated by calcium receptor activity. Diseases or disorder which can be treated by modulating other inorganic ion receptors can be identified in an analogous manner.

[0065] The inorganic ion receptor-modulating compounds of the present invention can exert an affect at an inorganic ion receptor causing one or more cellular effects ultimately producing a therapeutic effect. Calcium receptor-modulating compounds of the present invention can exert an effect on calcium receptor causing one or more cellular effects ultimately producing a therapeutic effect. Different diseases can be treated by the present invention by targeting cells having a calcium receptor.

[0066] For example, primary hyperparathyroidism (HPT) is characterized by hypercalcemia and abnormal elevated levels of circulating PTH. A defect associated with the major type of HPT is a diminished sensitivity of parathyroid cells to negative feedback regulation by extracellular Ca^{2+}. Thus, in tissue from patients with primary HPT, the "set-point" for extracellular Ca^{2+} is shifted to the right so that higher than normal concentrations of extracellular Ca^{2+} are required to depress PTH secretion. Moreover, in primary HPT, even high concentrations of extracellular Ca^{2+} often depress PTH secretion only partially. In secondary (uremic) HPT, a similar increase in the set-point for extracellular Ca^{2+} is observed even though the degree to which Ca^{2+} suppresses PTH secretion is normal. The changes in PTH secretion are paralleled by changes in $[Ca^{2+}]_i$: the set-point for extracellular Ca^{2+}-induced increases in $[Ca^{2+}]_i$ is shifted to the right and the magnitude of such increases is reduced.

[0067] Patients suffering from secondary HPT may also have renal osteodystrophy. Calcimimetics appear to be useful for treating both abnormal PTH secretion and osteodystrophy in such patients.

[0068] Compounds that mimic the action of extracellular Ca^{2+} are beneficial in the long-term management of both primary and secondary HPT. Such compounds provide the added impetus required to suppress PTH secretion which the hypercalcemic condition alone cannot achieve and, thereby, help to relieve the hypercalcemic condition. Compounds with greater efficacy than extracellular Ca^{2+} may overcome the apparent nonsuppressible component of PTH secretion which is particularly troublesome in the major form of primary HPT caused by adenoma of the parathyroid gland. Alternatively or additionally, such compounds can depress synthesis of PTH, as prolonged hypercalcemia has been shown to depress the levels of preproPTH mRNA in bovine and human adenomatous parathyroid tissue. Prolonged hypercalcemia also depresses parathyroid cell proliferation *in vitro*, so calcimimetics can also be effective in limiting the parathyroid cell hyperplasia characteristic of secondary HPT.

[0069] Cells other than parathyroid cells can respond directly to physiological changes in the concentration of extracellular Ca^{2+}. For example, calcitonin secretion from parafollicular cells in the thyroid (C-cells) is regulated by changes in the concentration of extracellular Ca^{2+}.

[0070] Isolated osteoclasts respond to increases in the concentration of extracellular Ca^{2+} with corresponding increases in $[Ca^{2-}]_i$ that arise partly from the mobilization of intracellular Ca^{2+}. Increases in $[Ca^{2+}]_i$ in osteoclasts are associated with the inhibition of bone resorption. Release of alkaline phosphatase from bone-forming osteoblasts is directly stimulated by calcium.

[0071] Renin secretion from juxtaglomerular cells in the kidney, like PTH secretion, is depressed by increased concentrations of extracellular Ca^{2+}. Extracellular Ca^{2+} causes the mobilization of intracellular Ca^{2+} in these cells. Other kidney cells respond to calcium as follows: elevated Ca^{2+} inhibits formation of $1,25(OH)_2$-vitamin D by proximal tubule cells, stimulates production of calcium-binding protein in distal tubule cells, and inhibits tubular reabsorption of Ca^{2+} and Mg^{2+} and the action of vasopressin on the thick ascending limb of Henle's loop (MTAL), reduces vasopressin action in the cortical collecting duct cells, and affects vascular smooth muscle cells in blood vessels of the renal glomerulus.

[0072] Calcium also promotes the differentiation of intestinal goblet cells, mammary cells, and skin cells; inhibits atrial natriuretic peptide secretion from cardiac atria; reduces cAMP accumulation in platelets; alters gastrin and glucagon secretion; acts on vascular smooth muscle cells to modify cell secretion of vasoactive factors; and affects cells of the central nervous system and peripheral nervous system.

[0073] Thus, there are sufficient indications to suggest that Ca^{2+} , in addition to its ubiquitous role as an intracellular signal, also functions as an extracellular signal to regulate the responses of certain specialized cells. Compounds of this invention can be used in the treatment of diseases or disorders associated with disrupted Ca^{2+} responses in these cells.

[0074] Specific diseases and disorders which might be treated or prevented, based upon the affected cells, also include those of the central nervous system such as seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and Tourette's syndrome; diseases involving excess water reabsorption by the kidney such as syndrome of inappropriate ADH secretion (SIADH), cirrhosis, congestive heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (*e.g.*, aminoglycoside antibiotics); gut motility disorders such as diarrhea, and spastic colon; GI ulcer diseases; GI diseases with excessive calcium absorption such as sarcoidosis; and autoimmune diseases and organ transplant rejection.

[0075] While calcium receptor-modulating compounds of the present invention will typically be used in therapy for human patients, they may also be used to treat similar or identical diseases in other warm-blooded animal species such as other primates, farm animals such as swine, cattle, and poultry; and sports animals and pets such as horses, dogs and cats.

IV. Administration

[0076] The different compounds described by the present invention can be used to treat different diseases or disorders by modulating inorganic ion receptor activity, preferably calcium receptor activity. The compounds of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA. Administration of ionomimetics and ionolytics is discussed by Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.

[0077] Suitable dosage forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such dosage forms should allow the compound to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological compounds or compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and dosage form which

retard the compound or composition from exerting its effect.

[0078] Compounds can also be formulated as pharmaceutically acceptable salts (*e.g.*, acid addition salts) and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts at the concentration at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristic of the compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

[0079] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. (*See e.g.,* PCT/US92/03736, hereby incorporated by reference herein.) Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, and quinic acid.

[0080] Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free base form of a compound is dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol solution, containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt is prepared by reacting the free base and acid in an organic solvent.

[0081] Carriers or excipients can also be used to facilitate administration of the compound. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. The compositions or pharmaceutical composition can be administered by different routes including intravenously, intraperitoneal, subcutaneous, and intramuscular, orally, topically, or transmucosaliy.

[0082] For systemic administration, oral administration is preferred. Alternatively, injection may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

[0083] Systemic administration can also be by transmucosal or transdermal means, or the compounds can be administered orally. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration may be through nasal sprays, for example, or using suppositories. For oral administration, the compounds can be formulated into conventional oral administration dosage forms such as capsules, tablets, and liquid preparations.

[0084] For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

[0085] The amounts of various compounds of this invention to be administered can be determined by standard procedures. Generally, a therapeutically effective amount is between about 1 nmole and 3 μmole of the compound, preferably 0.1 nmole and 1 μmole depending on its EC_{50} or IC_{50} and on the age and size of the patient, and the disease or disorder associated with the patient. Generally, it is an amount between about 0.1 and 50 mg/kg, preferably 0.01 and 20 mg/kg of the animal to be treated.

V. Examples

[0086] Examples are provided below illustrating different aspects and embodiments of the present invention.

Example 1: Cloning of Human Parathyroid Calcium Receptor From a Human Parathyroid Gland Adenoma Tumor

[0087] This example describes the cloning of a human parathyroid calcium receptor from a human parathyroid gland adenoma tumor using pBoPCaR1 as a hybridization probe (See, Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959). The probe was used to identify nucleic acid encoding human parathyroid gland calcium receptor by cross-hybridization at reduced stringency.

[0088] Messenger RNA was prepared from a human parathyroid gland adenoma tumor removed from a 39-year-old Caucasian male diagnosed with primary hyperparathyroidism. Northern blot analysis of this mRNA using pBoPCaR1 as a hybridization probe identified calcium receptor transcripts of about 5 Kb and about 4 Kb. A cDNA library was constructed from the mRNA. Double-stranded cDNA larger than 3 Kbp were size-selected on an agarose gel and ligated into the cloning vector lambda ZapII. Five hundred thousand primary recombinant phage were screened with the 5.2 Kbp cDNA insert of pBoPCaR1 as a hybridization probe. The pBoPCaR1 insert was labeled by random-primed synthesis

using [^{32}P]-dCTP to a specific activity of 1 x 10^9 cpm/μg.

[0089] Library screening was performed at a hybridization stringency of 400 mM Na^+, 50% formamide at a temperature of 38°C. Plaque lift filters were hybridized at a probe concentration of 500,000 cpm/ml for 20 hours. Following hybridization, filters were washed in 1 x SSC at 40°C for 1 hr.

[0090] The primary screen identified about 250 positive clones identified by hybridization to pBoPCaR1. Seven of these clones were taken through secondary and tertiary screens to isolate single clones that hybridized to the pBoPCaR1 probe. These seven clones were analyzed by restriction enzyme mapping and Southern blot analysis. Three of the clones contained cDNA inserts of about 5 Kbp and appear to be full-length clones corresponding to the 5 Kb mRNA. Two of the clones contain cDNA inserts of about 4 Kbp and appear to be full-length clones corresponding to the 4 Kb mRNA.

[0091] Restriction enzyme mapping of the two different sized inserts indicate that they share regions of sequence similarity in their 5' ends, but diverge in their 3' end sequences. DNA sequence analyses indicate that the smaller insert may result from alternative polyadenylation upstream of the polyadenylation site used in the larger insert.

[0092] Representative cDNA inserts for both size classes were subcloned into the plasmid vector pBluescript SK. Linearization followed by *in vitro* transcription using T7 RNA polymerase produced cRNA transcripts. The cRNA transcripts were injected into *Xenopus* oocytes (150 ng/μl RNA; 50 nl/oocyte) for functional analysis. Following incubation periods of 2-4 days, the oocytes were assayed for the presence of functional calcium receptors. Both clone types gave rise to functional calcium receptors as assessed by the stimulation of calcium-activated chloride currents upon addition of appropriate calcium receptor agonists. Known calcium receptor agonists, including NPS *R*-467 and NPS *R*-568 (see, Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959), activated the oocyte-expressed receptor at about the same concentrations known to be effective for the native parathyroid cell receptor. Thus, both clones encode a functional, human parathyroid cell calcium receptor.

[0093] Plasmids were prepared by subcloning each size class of insert into pBluescript thereby producing pHuPCaR 5.2 and pHuCaR 4.0. The nucleic acid sequence, and amino acid sequence, of the inserts are shown in SEQ. ID. Nos. 1 and 2.

[0094] Several differences were observed between the nucleic acid sequences of the two cDNA inserts. Sequence analyses of the two cDNA inserts indicate the existence of at least two sequence variants differing in the 3' untranslated' region and which may result from alternative polyadenylation. In addition, sequence variation exists at the 5' end of the inserts. These distinct sequences correspond to untranslated regions and may have arisen due to alternative transcriptional initiation and/or splicing.

[0095] Three additional sites of sequence variation are observed within the coding regions of cDNA clones pHuPCaR5.2 and pHuPCaR4.0 (see SEQ. ID. NOs. 1 and 2) demonstrating that these cDNA clones encode distinct proteins. Sequence analysis of the human CaR gene indicates that the additional 30 base pairs of DNA in cDNA clone pHuPCaR5.2, as compared to the pHuPCaR 4.0 cDNA clone, results from alternative mRNA splicing. The alternative mRNA splicing is predicted to insert 10 additional amino acids into the CaR polypeptide encoded by the pHuPCaR5.2 cDNA at a site between aa#536 and aa#537 in polypeptide encoded by pHuPCaR4.0 cDNA. In addition, pHuPCaR4.0 encodes glutamine (Gln) at aa#925 and glycine (Gly) at position 990 whereas pHuPCaR5.2 encodes arg (Arg) at both equivalent positions. The human CaR gene encodes for Gln and Arg, respectively, at these positions. The difference between the pHuPCaR4.0 cDNA compared to human DNA appears to represent a true sequence polymorphism within the human population while the single base change in pHuPCaR5.2 probably reflects a mutation which occurred during its cloning. Both cDNAs encode functional calcium receptors as demonstrated by the ability of *Xenopus* oocytes injected with cRNA prepared from these cDNA clones to respond to 10 mM extracellular calcium as ascertained by Cl- conductance. However, it is possible that these two receptor isoforms are functionally and/or pharmacologically distinct.

Example 2: Selection of Stable Recombinant Cells Expressing the Calcium Receptor

[0096] Clonal cell lines that stably express the two human and the bovine calcium receptors have been isolated. Calcium receptor cDNAs were subcloned in two different, commercially available expression vectors; pMSG (obtained from Pharmacia) and Cep4B (obtained from Invitrogen). The first vector contains the selectable marker gene for xanthine-guanine phosphoribosyltransferase (gpt) allowing stably transfected cells to overcome the blockade of the purine biosynthetic pathway imposed by addition of 2 μg/ml aminopterin and 25 μg/ml mycophenolic acid. The second' vector encodes a gene conferring resistance to the antibiotic hygromycin (used at 200 μg/ml). HuPCaR 5.2 and HuPCaR 4.0 cDNAs (SEQ. ID. NOs. 1 and 2, respectively) were removed from the parent bluescript plasmid with Not I and Hind III restriction enzymes and then either ligated directly into Not I + Hind III digested Cep4B or treated with the klenow fragment of DNA polymerase prior to blunt-end ligation into Sma I digested pMSG.

[0097] The pMSG subclone containing the HuPCaR 5.2 insert was transfected into CHO cells as discussed above. Selection has resulted in 20 resistant clones which are being characterized. The-Cep4B subclone containing the HuPCaR 5.2 insert was transfected into HEK 293 cells as described above. Selection with hygromycin resulted in a pool of stable clones. Clones expressing the HuPCaR 4.0 receptor isoform were prepared similarly.

[0098] Cells obtained from the pool of hygromycin selected HEK 293 cells transfected with Cep4B containing the HuPCaR 5.2 insert were plated on collagen coated Aklar squares which had been placed into individual wells of 12-well tissue culture plates. Two to six days later, medium was removed and the cells washed with balanced salt solution and 1 ml of buffer containing 1 μM fura2-AM, 1 mM $CaCl_2$ and 0.1% BSA and 1 mM $CaCl_2$. Measurements of fluorescence in response to calcium receptor agonists were performed at 37°C in a spectrofluorimeter using excitation and emission wavelengths of 340 and 510 nm, respectively. For signal calibration, Fmax was determined after addition of ionomycin (40 μM) and the apparent Fmin was determined by addition of 0.3 M EGTA, 2.5 M Tris-HCl; pH 10. Robust increases in $[Ca^{2+}]_i$ were observed in response to the addition of the following calcium receptor agonists: Ca^{2+} (10 mM), Mg^{2+} (20 mM) and NPS *R*-467. Control cells expressing functional substance K receptors did not respond to these calcimimetic compounds.

[0099] Additional clonal isolates of HEK 293 cells transfected with pHuPCaR4.0 sequence were obtained. These were tested for responsiveness to calcimimetics as described above except that the cells were tested while in suspension.

Example 3: Using Fura-2 Loaded Parathyroid cells To Measure to Calcium Receptor Activity

[0100] This section describes procedures used to obtain parathyroid cells from calves and humans, and to use the parathyroid cells to measure calcium receptor activity.

[0101] Parathyroid glands were obtained from freshly slaughtered calves (12-15 weeks old) at a local abattoir and transported to the laboratory in ice-cold parathyroid cell buffer (PCB) which contains (mM): NaCl, 126; KCl, 4; $MgCl_2$, 1; Na-HEPES, 20; pH 7.4; glucose, 5.6, and variable amounts of $CaCl_2$, *e.g.*, 1.25 mM. Human parathyroid glands, were obtained from patients undergoing surgical removal of parathyroid tissue for primary or uremic hyperparathyroidism (uremic HPT), and were treated similarly to bovine tissue.

[0102] Glands were trimmed of excess fat and connective tissue and then minced with fine scissors into cubes approximately 2-3 mm on a side. Dissociated parathyroid cells were prepared by collagenase digestion and then purified by centrifugation in Percoll buffer. The resultant parathyroid cell preparation was essentially devoid of red blood cells, adipocytes, and capillary tissue as assessed by phase contrast microscopy and Sudan black B staining. Dissociated and purified parathyroid cells were present as small clusters containing 5 to 20 cells. Cellular viability, as indexed by exclusion of trypan blue or ethidium bromide, was routinely 95%.

[0103] Although cells can be used for experimental purposes at this point, physiological responses (*e.g.,* suppressibility of PTH secretion and resting levels of $[Ca^{2+}]_i$) should be determined after culturing the cells overnight. Primary culture also has the advantage that cells can be labeled with isotopes to near isotopic equilibrium, as is necessary for studies involving measurements of inositol phosphate metabolism.

[0104] After purification on Percoll gradients, cells were washed several times in a 1:1 mixture of Ham's F12-Dulbecco's modified Eagle's medium (GIBCO) supplemented with 50 μg/ml streptomycin, 100 U/ml penicillin, 5 μg/ml gentamicin and ITS*. ITS* is a premixed solution containing insulin, transferrin, selenium, and bovine serum albumin (BSA)-linolenic acid (Collaborative Research, Bedford, MA). The cells were then transferred to plastic flasks (75 or 150 cm^2; Falcon) and incubated overnight at 37°C in a humid atmosphere of 5% CO_2. No serum is added to these overnight cultures, since its presence allows the cells to attach to the plastic, undergo proliferation, and dedifferentiate. Cells cultured under the above conditions were readily removed from the flasks by decanting, and show the same viability as freshly prepared cells.

[0105] Purified parathyroid cells were resuspended in 1.25 mM $CaCl_2$-2% BSA-PCB containing 1 μM fura-2-acetoxymethylester and incubated at 37°C for 20 minutes. The cells were then pelleted, resuspended in the same buffer, but lacking the ester, and incubated a further 15 minutes at 37°C. The cells were subsequently washed twice with PCB containing 0.5 mM $CaCl_2$ and 0.5% BSA and maintained at room temperature (about 20°C). Immediately before use, the cells were diluted five-fold with prewarmed 0.5 mM $CaCl_2$-PCB to obtain a final BSA concentration of 0.1%. The concentration of cells in the cuvette used for fluorescence recording was 1-2 x 10^6/ml.

[0106] The fluorescence of indicator-loaded cells was measured at 37°C in a spectrofluorimeter (Biomedical Instrumentation Group, University of Pennsylvania, Philadelphia, PA) equipped with a thermostated cuvette holder and magnetic stirrer using excitation and emission wavelengths of 340 and 510 nm, respectively. This fluorescence indicates the level of cytosolic Ca^{2+}. Fluorescence signals were calibrated using digitonin (50 μg/ml, final) to obtain maximum fluorescence (F_{max}), and EGTA (10 mM, pH 8.3, final) to obtain minimal fluorescence (F_{min}), and a dissociation constant of 224 nM. Leakage of dye is dependent on temperature and most occurs within the first 2 minutes after warming the cells in the cuvette. Dye leakage increases only very slowly thereafter. To correct the calibration for dye leakage, cells were placed in the cuvette and stirred at 37°C for 2-3 minutes. The cell suspension was then removed, the cells pelleted, and the supernatant returned to a clean cuvette. The supernatant was then treated with digitonin and EGTA to estimate dye leakage, which is typically 10-15% of the total Ca^{2+}-dependent fluorescent signal. This estimate was subtracted from the apparent F_{min}.

Example 4: Using Fura-2 Loaded HEK 293/pHuPCaR4.0 Cells To Measure to Calcium Receptor Activity

[0107] This section describes procedures used to assay calcium receptor activity using fura-2 loaded HEK 293/pHuPCaR4.0 cells. HEK 293 cells transfected with pHuPCaR4.0 were loaded with fura-2 by incubating the cells in Dulbecco's modified Eagle's media buffered with 20 mM HEPES containing about 5 μM fluo-3/AM for one hour at room temperature. Cell were then rinsed with Hank's balanced salt solution buffered with 20 mM HEPES containing 1 mM $CaCl_2$ and 1 mM $MgCl_2$. Compounds to be tested were then added to the cells and fluorescence was measured (excitation and emission wavelengths of 340 and 510 nm, respectively).

Example 5: Measuring the Ability of Compounds to Modulate Calcium Receptor Activity

[0108] The ability of different compounds to modulate calcium receptor activity was assayed by measuring increases in $[Ca^{2+}]_i$ in HEK 293 cells transfected with nucleic acid encoding pHuPCaR4.0 using fura-2 loaded cells or using parathyroid cells loaded with using fura-2 loaded cells. Results of different experiments are summarized in Tables 1.a, 1.b.1, 1.b.2, 1.c., and 2. Tables 1.a, 1.b.1, 1.b.2, and 1.c summarizes the effects of compounds, at different concentrations, on calcium receptor activity assayed as described in Example 4 (*i.e.*, using HEK 293 cells transfected with nucleic acid encoding pHuPCaR4.0, which were loaded with fura-2).

[0109] Table 2, summarizes the results of different experiments where the EC_{50} was calculated either parathyroid cells, or HEK 293/pHuPCaR4.0, loaded with fura-2. Cells were loaded with fura-2 and assayed as described in Example 2 (for parathyroid cells) or Example 3 (for HEK 293/pHuPCaR4.0 cells).

Table 1.a. Calcimimetic compounds which produce greater than 40% response at 3.3 ng/mL in HEK-293 cells expressing the human calcium receptor.

Compound Code	% activity at four concentrations (ng/mL)			
	3300	330	33	3.3
Reference compounds				
R-568		95	69	24
25G	130	115	99	66
12F	118	110	101	63
25H	115	107	89	45

Table 1.b.1. Calcimimetic compounds which produce greater than 40% response at 33 ng/mL in HEK-293 cells expressing the human calcium receptor

Compound Code	% activity at four concentrations (ng/mL)			
	3300	330	33	3.3
Reference compounds				
R-568		95	69	24
12C	134	125	98	39
12G	139	139	81	35
12E	117	121	73	23

Table 1.b.2 Calcimimetic compounds which produce greater than 40% response at 33 ng/mL in HEK-293 cells expressing the human calcium receptor

Compound Code	% activity at four concentrations (ng/mL)			
	3300	330	33	3.3
reference compounds				
R568		95	69	24

(continued)

Compound Code	% activity at four concentrations (ng/mL)			
	3300	330	33	3.3
12B	130	110	56	4
8T		85	55	13
12D	128	109	52	5

Table 1.c. Calcimimetic compounds which produce greater than 40% response at 330 ng/mL in HEK-293 cells expressing the human calcium receptor

Compound Code	% activity at four concentrations (ng/mL)			
	3300	330	33	3.3
reference compounds				
R568		95	69	24

TABLE 2

Arylalkylamine Calcimimetics from Figure 1 Active at the Parathyroid Cell Calcium Receptor *In Vitro* ($EC_{50} \leq 5$ μM)			
Compound Code (from Fig. 1)	EC_{50} (μM)	Compound Code (from Fig. 1)	EC_{50} (μM)
NPS *R*-467	2.0		
NPS *R*-568	0.60		
		12Z not claimed	0.11
8T	1.8		
11D	1.8		

Examples Synthesis of Compounds

[0110] The compounds described herein can be synthesized using standard techniques such as those described by Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959. Examples describing representative syntheses of compounds described in the text are provided below.

[0111] Compound 12Z not claimed as prepared by a diisobutylaluminum hydride (DIBAL-H) mediated condensation of an amine with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.

[0112] The amines in these syntheses were purchased from Aldrich Chemical Co., Milwaukee, WI, or from Celgene Corp., Warren, NJ, or were prepared synthetically using standard techniques. All other reagent chemicals were purchased from Aldrich Chemical Co.

Preparation of 12Z not claimed

[0113] A stirred solution of 2-chlorohydrocinnamonitrile (Aldrich Chemical Co., 1.66 g, 10 mmol) in dichloromethane (100 ml) was cooled to -78°C and treated dropwise with diisobutylaluminum hydride (1.42 g, 10 mmol). The reaction was stirred 1 hr at rt, cooled to -78 °C and treated with a solution of 1-(1-naphthyl)ethylamine (1.71 g, 10 mmol) in dichloromethane (25 ml). The reaction was transferred to an ice bath and stirred 2 hr. After this time the reaction was poured directly into a stirred solution of ethanolic sodium borohydride (50 ml of 0.2 M, 10 mmol). The mixture was stirred 30 min at rt and the excess sodium borohydride quenched by the addition of 10% HCl. The solution was then made basic by the addition of 10 N NaOH and transferred to a separatory funnel washing with diethyl ether (300 ml). The aqueous phase was removed and the remaining organic layer washed with 1 *N* NaOH (3 x 100 ml) . The organic layer was dried over anhydrous magnesium sulfate, and concentrated to an oil. Chromatography of this material through silica gel using a gradient of chloroform to 10% methanol-chloroform afforded 2.34g (72% yield) of (*R*)-N-[3-(2-chlorophenyl) propyl]-1-(1-naphthyl)ethylamine, 12Z, as a clear oil; m/z (rel. int.) 323 (M+, 2), 308 (63), 288 (7), 196 (5), 184 (5), 155

(100), 125 (24), 115 (8), 103 (4), 91 (3), 77 (7) .

Preparation of 12B

[0114] In a similar fashion, 4-methylcinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (*R*)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatography yielded (*R*)-*N*-[3-(4-methylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamine, 12B, as a clear, colorless oil; m/z (rel. int.) 281 (M+, 6), 266 (5), 176 (27), 146 (75), 135 (63), 131 (100), 115 (25), 105 (21), 91 (21), 77 (21).

Preparation of 12C

[0115] In a similar fashion, 2-methylcinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (*R*)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatography yielded (*R*)-*N*-[3-(2-methylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamine, 12C, as a clear, colorless oil; m/z (rel. int.) 281 (M+, 4), 266 (15), 176 (18), 146 (62), 135 (58), 131 (100), 115 (23), 105 (19), 91 (38), 77 (17).

Preparation of 12D

[0116] In a similar fashion, 2,4,6-trimethylcinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (*R*)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatography yielded (*R*)-*N*-[3-(2,4,6-trimethylphenyl) prop-2-enyl]-1-(3-methoxyphenyl)ethylamine, 12D, as a clear, colorless oil; m/z (rel. int.) 309 (M+,8), 294 (25), 174 (82), 159 (100), 135 (52), 129 (29), 105 (21), 91 (17), 77 (14) .

Preparation of 12E

[0117] In a similar fashion, 4-isopropylcinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (R)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatographyyielded (R)-N-[3-(4-isopropylphenyl) prop-2-enyl]-1-(3-methoxyphenyl)ethylamine, 12E, as a clear, colorless oil; m/z (rel. int.) 309 (M^+, 9), 294 (7), 174 (98), 159 (22), 135 (80), 117 (100), 105 (35), 91 (37), 77 (19) .

Preparation of 12F

[0118] In a similar fashion, 2,4-dimethylcinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (R)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatography yielded (R)-N-[3-(2,4-dimethylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamine, 12F, as a clear, colorless oil; m/z (rel. int.) 295 (M^+, 8), 294 (15), 174 (29), 160 (75), 145 (100), 135 (68), 117 (21), 105 (30), 91 (26), 77 (19) .

Preparation of 12G

[0119] In a similar fashion, 3-methylcinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (R)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatography yielded (R)-N-[3-(3-methylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamine, 12G, as a clear, colorless oil; m/z (rel. int.) 281 (M^+, 5), 266 (9), 176 (24), 146 (71), 135 (62), 131 (100), 115 (23), 105 (19), 91 (41), 77 (18) .

Preparation of 25E

[0120] In a similar fashion, cinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (R)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatography yielded (R)-N-(3-phenylprop-2-enyl)-1-(3-methoxyphenyl)ethylamine, 25E, as a clear colorless oil; m/z (rel. int.) 267 (M^+, 3), 252 (14), 176 (17), 135 (62), 117 (100), 105 (28), 91 (56), 77 (33).

Preparation of 25G

[0121] In a similar fashion, α-methylcinnamonitrile was treated with diisobutyl aluminum hydride and the intermediate aluminum-imine complex treated with (R)-1-(3-methoxyphenyl)ethylamine. The intermediate imine was treated with ethanolic sodium borohydride. Work-up and chromatography yielded (*R*)-*N*-(2-methyl-3-phenylprop-2-enyl)-1-(3-methoxyphenyl)ethylamine, 25G, as a clear, colorless oil; m/z (rel. int.) 281 (M+,5), 266 (18), 190 (12), 146 (78), 135 (82), 131 (100), 115 (21), 105 (21), 91 (62), 77 (19).

Example 19: Pharmaceutical Formulation

[0122] Preparation of a pharmaceutical formulation suitable for administering a calcimimetic into a human patient is shown in Table 3.

TABLE 3

Ingredient	mg/capsule	g/representative batch of 5,000 capsules
NPS *R*-568	56.0	280.0
Pregelatinized Starch NF	134.0	670.0
Microcrystalline Cellulose NF	34.0	170.0
Colloidal Silicon Dioxide	1.0	5.0
Total	225 mg	1125 g

Other examples of NPS (*R*)-568 hydrochloride formulations and dosage forms include those suitable for sustained or extended release, using standard techniques.

[0123] Proper dosing can also be carried out using standard techniques. For example, in one set of experiments, 10 - 400 mg oral doses of NPS (*R*)-568 hydrochloride showed pharmacological activity in human subjects. Significant levels of the *O*-glucuronide conjugate of 17Q, a principal metabolite of NPS (*R*)-568, was observed in human plasma following oral administration of NPS (*R*)-568 hydrochloride. Thus, the glucuronide conjugate of 17Q may be exerting some beneficial effect.

[0124] Using standard techniques other suitable dosage ranges for NPS (*R*)-568 can be determined.

[0125] Suitable dosage ranges, formulations, and dosage forms for other compounds described herein can also be determined by one skilled in art based on the teachings provided in the application.

SEQUENCE LISTING

[0126]

(1) GENERAL INFORMATION:

(i) APPLICANT: NPS Pharmaceuticals, Inc.

(ii) TITLE OF INVENTION: CALCIUM RECEPTOR-ACTIVE COMPOUNDS

(iii) NUMBER OF SEQUENCES: 2

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Lyon & Lyon
(B) STREET: First Interstate World Center, Suite 4700 633 West Fifth Street
(C) CITY: Los Angeles
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 90017

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: 3.5" Diskette, 1.44 Mb storage
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: FastSeq

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

Prior applications total,
including application
described below: 2

(A) APPLICATION NUMBER: U.S. 08/353,784
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(B) FILING DATE: 21 October, 1994

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Heber, Sheldon O.
(B) REGISTRATION NUMBER: 38,179
(C) REFERENCE/DOCKET NUMBER: 215/304

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (213) 489-1600
(B) TELEFAX: (213) 955-0440
(C) TELEX: 67-3510

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5006 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA
(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 436..3699
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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GCTGCTGTGG CCGGACCCGA AGGCGGGCGC CGGGAGCGCA                40

GCGAGCCAGA CGCGCCTCTC CAAGACCGTG ACCTTGGCAT                80

AGGGAGCGGG GCTGCGCGCA GTCCTGAGAT CAGACCAGAG               120

CTCATCCTCG TGGAGACCCA CGGCCGAGGG GCCGGAGCTG               160

CCTCTGTGCG AGGGAGCCCT GGCCGCGGCG CAGAAGGCAT               200

CACAGGAGGC CTCTGCATGA TGTGGCTTCC AAAGACTCAA               240

GGACCACCCA CATTACAAGT CTGGATTGAG GAAGGCAGAA               280

ATGGAGATTC AAACACCACG TCTTCTATTA TTTTATTAAT               320

CAATCTGTAG ACATGTGTCC CCACTGCAGG GAGTGAACTG               360

CTCCAAGGGA GAAACTTCTG GGAGCCTCCA AACTCCTAGC               400

TGTCTCATCC CTTGCCCTGG AGAGACGGCA GAACC                    435

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Met Ala Phe Tyr Ser Cys Cys Trp Val Leu Leu Ala
  1               5                  10
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CTC ACC TGG CAC ACC TCT GCC TAC GGG CCA GAC CAG          507
Leu Thr Trp His Thr Ser Ala Tyr Gly Pro Asp Gln
          15                  20

CGA GCC CAA AAG AAG GGG GAC ATT ATC CTT GGG GGG          543
Arg Ala Gln Lys Lys Gly Asp Ile Ile Leu Gly Gly
 25                  30                  35

CTC TTT CCT ATT CAT TTT GGA GTA GCA GCT AAA GAT          579
Leu Phe Pro Ile His Phe Gly Val Ala Ala Lys Asp
             40                  45

CAA GAT CTC AAA TCA AGG CCG GAG TCT GTG GAA TGT          615
Gln Asp Leu Lys Ser Arg Pro Glu Ser Val Glu Cys
     50                  55                  60

ATC AGG TAT AAT TTC CGT GGG TTT CGC TGG TTA CAG          651
Ile Arg Tyr Asn Phe Arg Gly Phe Arg Trp Leu Gln
                 65                  70

GCT ATG ATA TTT GCC ATA GAG GAG ATA AAC AGC AGC          687
Ala Met Ile Phe Ala Ile Glu Glu Ile Asn Ser Ser
          75                  80

CCA GCC CTT CTT CCC AAC TTG ACG CTG GGA TAC AGG          723
Pro Ala Leu Leu Pro Asn Leu Thr Leu Gly Tyr Arg
 85                  90                  95

ATA TTT GAC ACT TGC AAC ACC GTT TCT AAG GCC TTG          759
Ile Phe Asp Thr Cys Asn Thr Val Ser Lys Ala Leu
             100                 105

GAA GCC ACC CTG AGT TTT GTT GCT CAA AAC AAA ATT          795
Glu Ala Thr Leu Ser Phe Val Ala Gln Asn Lys Ile
     110                 115                 120

GAT TCT TTG AAC CTT GAT GAG TTC TGC AAC TGC TCA          831
Asp Ser Leu Asn Leu Asp Glu Phe Cys Asn Cys Ser
                 125                 130

GAG CAC ATT CCC TCT ACG ATT GCT GTG GTG GGA GCA          867
Glu His Ile Pro Ser Thr Ile Ala Val Val Gly Ala
          135                 140

ACT GGC TCA GGC GTC TCC ACG GCA GTG GCA AAT CTG          903
Thr Gly Ser Gly Val Ser Thr Ala Val Ala Asn Leu
145                 150                 155

CTG GGG CTC TTC TAC ATT CCC CAG GTC AGT TAT GCC          939
Leu Gly Leu Phe Tyr Ile Pro Gln Val Ser Tyr Ala
             160                 165

TCC TCC AGC AGA CTC CTC AGC AAC AAG AAT CAA TTC          975
Ser Ser Ser Arg Leu Leu Ser Asn Lys Asn Gln Phe
     170                 175                 180
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Lys Ser Phe Leu Arg Thr Ile Pro Asn Asp Glu His
                185                 190

CAG GCC ACT GCC ATG GCA GAC ATC ATC GAG TAT TTC      1047
Gln Ala Thr Ala Met Ala Asp Ile Ile Glu Tyr Phe
        195                 200

CGC TGG AAC TGG GTG GGC ACA ATT GCA GCT GAT GAC      1083
Arg Trp Asn Trp Val Gly Thr Ile Ala Ala Asp Asp
205                 210                 215

GAC TAT GGG CGG CCG GGG ATT GAG AAA TTC CGA GAG      1119
Asp Tyr Gly Arg Pro Gly Ile Glu Lys Phe Arg Glu
                220                 225

GAA GCT GAG GAA AGG GAT ATC TGC ATC GAC TTC AGT      1155
Glu Ala Glu Glu Arg Asp Ile Cys Ile Asp Phe Ser
    230                 235                 240

GAA CTC ATC TCC CAG TAC TCT GAT GAG GAA GAG ATC      1191
Glu Leu Ile Ser Gln Tyr Ser Asp Glu Glu Glu Ile
                245                 250

CAG CAT GTG GTA GAG GTG ATT CAA AAT TCC ACG GCC      1227
Gln His Val Val Glu Val Ile Gln Asn Ser Thr Ala
        255                 260

AAA GTC ATC GTG GTT TTC TCC AGT GGC CCA GAT CTT      1263
Lys Val Ile Val Val Phe Ser Ser Gly Pro Asp Leu
265                 270                 275

GAG CCC CTC ATC AAG GAG ATT GTC CGG CGC AAT ATC      1299
Glu Pro Leu Ile Lys Glu Ile Val Arg Arg Asn Ile
                280                 285

ACG GGC AAG ATC TGG CTG GCC AGC GAG GCC TGG GCC      1335
Thr Gly Lys Ile Trp Leu Ala Ser Glu Ala Trp Ala
    290                 295                 300

AGC TCC TCC CTG ATC GCC ATG CCT CAG TAC TTC CAC      1371
Ser Ser Ser Leu Ile Ala Met Pro Gln Tyr Phe His
                305                 310

GTG GTT GGC GGC ACC ATT GGA TTC GCT CTG AAG GCT      1407
Val Val Gly Gly Thr Ile Gly Phe Ala Leu Lys Ala
        315                 320

GGG CAG ATC CCA GGC TTC CGG GAA TTC CTG AAG AAG      1443
Gly Gln Ile Pro Gly Phe Arg Glu Phe Leu Lys Lys
325                 330                 335

GTC CAT CCC AGG AAG TCT GTC CAC AAT GGT TTT GCC      1479
Val His Pro Arg Lys Ser Val His Asn Gly Phe Ala
                340                 345
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AAG GAG TTT TGG GAA GAA ACA TTT AAC TGC CAC CTC      1515
Lys Glu Phe Trp Glu Glu Thr Phe Asn Cys His Leu
    350                 355                 360

CAA GAA GGT GCA AAA GGA CCT TTA CCT GTG GAC ACC      1551
Gln Glu Gly Ala Lys Gly Pro Leu Pro Val Asp Thr
                365                 370

TTT CTG AGA GGT CAC GAA GAA AGT GGC GAC AGG TTT      1587
Phe Leu Arg Gly His Glu Glu Ser Gly Asp Arg Phe
        375                 380

AGC AAC AGC TCG ACA GCC TTC CGA CCC CTC TGT ACA      1623
Ser Asn Ser Ser Thr Ala Phe Arg Pro Leu Cys Thr
385                 390                 395

GGG GAT GAG AAC ATC AGC AGT GTC GAG ACC CCT TAC      1659
Gly Asp Glu Asn Ile Ser Ser Val Glu Thr Pro Tyr
            400                 405

ATA GAT TAC ACG CAT TTA CGG ATA TCC TAC AAT GTG      1695
Ile Asp Tyr Thr His Leu Arg Ile Ser Tyr Asn Val
    410                 415                 420

TAC TTA GCA GTC TAC TCC ATT GCC CAC GCC TTG CAA      1731
Tyr Leu Ala Val Tyr Ser Ile Ala His Ala Leu Gln
                425                 430

GAT ATA TAT ACC TGC TTA CCT GGG AGA GGG CTC TTC      1767
Asp Ile Tyr Thr Cys Leu Pro Gly Arg Gly Leu Phe
        435                 440

ACC AAT GGC TCC TGT GCA GAC ATC AAG AAA GTT GAG      1803
Thr Asn Gly Ser Cys Ala Asp Ile Lys Lys Val Glu
445                 450                 455

GCG TGG CAG GTC CTG AAG CAC CTA CGG CAT CTA AAC      1839
Ala Trp Gln Val Leu Lys His Leu Arg His Leu Asn
            460                 465

TTT ACA AAC AAT ATG GGG GAG CAG GTG ACC TTT GAT      1875
Phe Thr Asn Asn Met Gly Glu Gln Val Thr Phe Asp
    470                 475                 480

GAG TGT GGT GAC CTG GTG GGG AAC TAT TCC ATC ATC      1911
Glu Cys Gly Asp Leu Val Gly Asn Tyr Ser Ile Ile
                485                 490

AAC TGG CAC CTC TCC CCA GAG GAT GGC TCC ATC GTG      1947
Asn Trp His Leu Ser Pro Glu Asp Gly Ser Ile Val
        495                 500

TTT AAG GAA GTC GGG TAT TAC AAC GTC TAT GCC AAG      1983
Phe Lys Glu Val Gly Tyr Tyr Asn Val Tyr Ala Lys
505                 510                 515
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AAG GGA GAA AGA CTC TTC ATC AAC GAG GAG AAA ATC      2019
Lys Gly Glu Arg Leu Phe Ile Asn Glu Glu Lys Ile
            520                 525

CTG TGG AGT GGG TTC TCC AGG GAG CCA CTC ACC TTT      2055
Leu Trp Ser Gly Phe Ser Arg Glu Pro Leu Thr Phe
    530                 535                 540

GTG CTG TCT GTC CTC CAG GTG CCC TTC TCC AAC TGC      2091
Val Leu Ser Val Leu Gln Val Pro Phe Ser Asn Cys
                545                 550

AGC CGA GAC TGC CTG GCA GGG ACC AGG AAA GGG ATC      2127
Ser Arg Asp Cys Leu Ala Gly Thr Arg Lys Gly Ile
        555                 560

ATT GAG GGG GAG CCC ACC TGC TGC TTT GAG TGT GTG      2163
Ile Glu Gly Glu Pro Thr Cys Cys Phe Glu Cys Val
565                 570                 575

GAG TGT CCT GAT GGG GAG TAT AGT GAT GAG ACA GAT      2199
Glu Cys Pro Asp Gly Glu Tyr Ser Asp Glu Thr Asp
            580                 585

GCC AGT GCC TGT AAC AAG TGC CCA GAT GAC TTC TGG      2235
Ala Ser Ala Cys Asn Lys Cys Pro Asp Asp Phe Trp
    590                 595                 600

TCC AAT GAG AAC CAC ACC TCC TGC ATT GCC AAG GAG      2271
Ser Asn Glu Asn His Thr Ser Cys Ile Ala Lys Glu
                605                 610

ATC GAG TTT CTG TCG TGG ACG GAG CCC TTT GGG ATC      2307
Ile Glu Phe Leu Ser Trp Thr Glu Pro Phe Gly Ile
        615                 620

GCA CTC ACC CTC TTT GCC GTG CTG GGC ATT TTC CTG      2343
Ala Leu Thr Leu Phe Ala Val Leu Gly Ile Phe Leu
625                 630                 635

ACA GCC TTT GTG CTG GGT GTG TTT ATC AAG TTC CGC      2379
Thr Ala Phe Val Leu Gly Val Phe Ile Lys Phe Arg
            640                 645

AAC ACA CCC ATT GTC AAG GCC ACC AAC CGA GAG CTC      2415
Asn Thr Pro Ile Val Lys Ala Thr Asn Arg Glu Leu
    650                 655                 660

TCC TAC CTC CTC CTC TTC TCC CTG CTC TGC TGC TTC      2451
Ser Tyr Leu Leu Leu Phe Ser Leu Leu Cys Cys Phe
                665                 670

TCC AGC TCC CTG TTC TTC ATC GGG GAG CCC CAG GAC      2487
Ser Ser Ser Leu Phe Phe Ile Gly Glu Pro Gln Asp
        675                 680
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TGG ACG TGC CGC CTG CGC CAG CCG GCC TTT GGC ATC      2523
Trp Thr Cys Arg Leu Arg Gln Pro Ala Phe Gly Ile
685                 690                 695

AGC TTC GTG CTC TGC ATC TCA TGC ATC CTG GTG AAA      2559
Ser Phe Val Leu Cys Ile Ser Cys Ile Leu Val Lys
            700                 705

ACC AAC CGT GTC CTC CTG GTG TTT GAG GCC AAG ATC      2595
Thr Asn Arg Val Leu Leu Val Phe Glu Ala Lys Ile
    710                 715                 720

CCC ACC AGC TTC CAC CGC AAG TGG TGG GGG CTC AAC      2631
Pro Thr Ser Phe His Arg Lys Trp Trp Gly Leu Asn
                725                 730

CTG CAG TTC CTG CTG GTT TTC CTC TGC ACC TTC ATG      2667
Leu Gln Phe Leu Leu Val Phe Leu Cys Thr Phe Met
        735                 740

CAG ATT GTC ATC TGT GTG ATC TGG CTC TAC ACC GCG      2703
Gln Ile Val Ile Cys Val Ile Trp Leu Tyr Thr Ala
745                 750                 755

CCC CCC TCA AGC TAC CGC AAC CAG GAG CTG GAG GAT      2739
Pro Pro Ser Ser Tyr Arg Asn Gln Glu Leu Glu Asp
            760                 765

GAG ATC ATC TTC ATC ACG TGC CAC GAG GGC TCC CTC      2775
Glu Ile Ile Phe Ile Thr Cys His Glu Gly Ser Leu
    770                 775                 780

ATG GCC CTG GGC TTC CTG ATC GGC TAC ACC TGC CTG      2811
Met Ala Leu Gly Phe Leu Ile Gly Tyr Thr Cys Leu
                785                 790

CTG GCT GCC ATC TGC TTC TTC TTT GCC TTC AAG TCC      2847
Leu Ala Ala Ile Cys Phe Phe Phe Ala Phe Lys Ser
        795                 800

CGG AAG CTG CCG GAG AAC TTC AAT GAA GCC AAG TTC      2883
Arg Lys Leu Pro Glu Asn Phe Asn Glu Ala Lys Phe
805                 810                 815

ATC ACC TTC AGC ATG CTC ATC TTC TTC ATC GTC TGG      2919
Ile Thr Phe Ser Met Leu Ile Phe Phe Ile Val Trp
            820                 825

ATC TCC TTC ATT CCA GCC TAT GCC AGC ACC TAT GGC      2955
Ile Ser Phe Ile Pro Ala Tyr Ala Ser Thr Tyr Gly
    830                 835                 840

AAG TTT GTC TCT GCC GTA GAG GTG ATT GCC ATC CTG      2991
Lys Phe Val Ser Ala Val Glu Val Ile Ala Ile Leu
                845                 850
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GCA GCC AGC TTT GGC TTG CTG GCG TGC ATC TTC TTC      3027
Ala Ala Ser Phe Gly Leu Leu Ala Cys Ile Phe Phe
        855                 860

AAC AAG ATC TAC ATC ATT CTC TTC AAG CCA TCC CGC      3063
Asn Lys Ile Tyr Ile Ile Leu Phe Lys Pro Ser Arg
865                 870                 875

AAC ACC ATC GAG GAG GTG CGT TGC AGC ACC GCA GCT      3099
Asn Thr Ile Glu Glu Val Arg Cys Ser Thr Ala Ala
            880                 885

CAC GCT TTC AAG GTG GCT GCC CGG GCC ACG CTG CGC      3135
His Ala Phe Lys Val Ala Ala Arg Ala Thr Leu Arg
    890                 895                 900

CGC AGC AAC GTC TCC CGC AAG CGG TCC AGC AGC CTT      3171
Arg Ser Asn Val Ser Arg Lys Arg Ser Ser Ser Leu
                905                 910

GGA GGC TCC ACG GGA TCC ACC CCC TCC TCC TCC ATC      3207
Gly Gly Ser Thr Gly Ser Thr Pro Ser Ser Ser Ile
        915                 920

AGC AGC AAG AGC AAC AGC GAA GAC CCA TTC CCA CGG      3243
Ser Ser Lys Ser Asn Ser Glu Asp Pro Phe Pro Arg
925                 930                 935

CCC GAG AGG CAG AAG CAG CAG CAG CCG CTG GCC CTA      3279
Pro Glu Arg Gln Lys Gln Gln Gln Pro Leu Ala Leu
            940                 945

ACC CAG CAA GAG CAG CAG CAG CAG CCC CTG ACC CTC      3315
Thr Gln Gln Glu Gln Gln Gln Gln Pro Leu Thr Leu
    950                 955                 960

CCA CAG CAG CAA CGA TCT CAG CAG CAG CCC AGA TGC      3351
Pro Gln Gln Gln Arg Ser Gln Gln Gln Pro Arg Cys
                965                 970

AAG CAG AAG GTC ATC TTT GGC AGC GGC ACG GTC ACC      3387
Lys Gln Lys Val Ile Phe Gly Ser Gly Thr Val Thr
        975                 980

TTC TCA CTG AGC TTT GAT GAG CCT CAG AAG AAC GCC      3423
Phe Ser Leu Ser Phe Asp Glu Pro Gln Lys Asn Ala
985                 990                 995

ATG GCC CAC AGG AAT TCT ACG CAC CAG AAC TCC CTG      3459
Met Ala His Arg Asn Ser Thr His Gln Asn Ser Leu
            1000                1005

GAG GCC CAG AAA AGC AGC GAT ACG CTG ACC CGA CAC      3495
Glu Ala Gln Lys Ser Ser Asp Thr Leu Thr Arg His
    1010                1015                1020
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CAG CCA TTA CTC CCG CTG CAG TGC GGG GAA ACG GAC      3531
Gln Pro Leu Leu Pro Leu Gln Cys Gly Glu Thr Asp
                1025                1030

TTA GAT CTG ACC GTC CAG GAA ACA GGT CTG CAA GGA      3567
Leu Asp Leu Thr Val Gln Glu Thr Gly Leu Gln Gly
        1035                1040

CCT GTG GGT GGA GAC CAG CGG CCA GAG GTG GAG GAC      3603
Pro Val Gly Gly Asp Gln Arg Pro Glu Val Glu Asp
1045                1050                1055

CCT GAA GAG TTG TCC CCA GCA CTT GTA GTG TCC AGT      3639
Pro Glu Glu Leu Ser Pro Ala Leu Val Val Ser Ser
            1060                1065

TCA CAG AGC TTT GTC ATC AGT GGT GGA GGC AGC ACT      3675
Ser Gln Ser Phe Val Ile Ser Gly Gly Gly Ser Thr
    1070                1075                1080

GTT ACA GAA AAC GTA GTG AAT TCA TAAAATGGAA           3709
Val Thr Glu Asn Val Val Asn Ser
                1085

GGAGAAGACT GGGCTAGGGA GAATGCAGAG AGGTTTCTTG          3749

GGGTCCCAGG GATGAGGAAT CGCCCCAGAC TCCTTTCCTC          3789

TGAGGAAGAA GGGATAATAG ACACATCAAA TGCCCCGAAT          3829

TTAGTCACAC CATCTTAAAT GACAGTGAAT TGACCCATGT          3869

TCCCTTTAAA ATTAAAAAAA AGAAGAGCCT TGTGTTTCTG          3909

TGGTTGCATT TGTCAAAGCA TTGAGATCTC CACGGTCAGA          3949

TTTGCTGTTC ACCCACATCT AATGTCTCTT CCTCTGTTCT          3989

ATCCCACCCA ACAGCTCAGA GATGAAACTA TGGCTTTAAA          4029

CTACCCTCCA GAGTGTGCAG ACTGATGGGA CATCAAATTT          4069

GCCACCACTA GAGCTGAGAG TCTGAAAGAC AGAATGTCAC          4109

CAGTCCTGCC CAATGCCTTG ACAACAGACT GAATTTTAAA          4149

TGTTCACAAC ATAAGGAGAA TGTATCTCCT CCTATTTATG          4189

AAAACCATAT GATATTTTGT CTCCTACCTG CTGCTGCTAT          4229

TATGTAACAT CCAGAAGGTT TGCACCCCTC CTATACCATA          4269

TGTCTGGTTC TGTCCAGGAC ATGATACTGA TGCCATGTTT          4309

AGATTCCAGG ATCACAAGAA TCACCTCAAA TTGTTAGGAA          4349
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GGGACTGCAT AAACCAATGA GCTGTATCTG TAATTAATAT 4389

TCCTATATGT AGCTTTATCC TTAGGAAAAT GCTTCTGTTG 4429

TAATAGTCCA TGGACAATAT AAACTGAAAA ATGTCAGTCT 4469

GGTTTATATA AGGCAGTATT ATTGAGCTCT ATTTCCCCAC 4509

CCCACTATCC TCACTCCCAT AAGCTAAGCC TTATGTGAGC 4549

CCCTTCAGGG ACTCAAGGGT CCAGAAGTCC CTCCCATCTC 4589

TACCCCAAAG AATTCCTGAA GCCAGATCCA CCCTATCCCT 4629

GTACAGAGTA AGTTCTCAAT TATTGGCCTG CTAATAGCTG 4669

CTAGGGTAGG AAAGCGTGGT TCCAAGAAAG ATCCACCCTC 4709

AAATGTCGGA GCTATGTTCC CTCCAGCAGT GGTATTAATA 4749

CTGCCGGTCA CCCAGGCTCT GGAGCCAGAG AGACAGACCG 4789

GGGTTCAAGC CATGGCTTCG TCATTTGCAA GCTGAGTGAC 4829

TGTAGGCAGG GAACCTTAAC CTCTCTAAGC CACAGCTTCT 4869

TCATCTTTAA AATAAGGATA ATAATCATTC CTTCCCCTCA 4909

GAGCTCTTAT GTGGATTAAA CGAGATAATG TATATAAAGT 4949

ACTTTAGCCT GGTACCTAGC ACACAATAAG CATTCAATAA 4989

ATATTAGTTA ATATTAT 5006

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3809 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA
(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 373..3606
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:
CAACAGGCAC CTGGCTGCAG CCAGGAAGGA CCGCACGCCC 40

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TGCAGAATGA AAGGCATCAC AGGAGGCCTC TGCATGATGT                         160

GGCTTCCAAA GACTCAAGGA CCACCCACAT TACAAGTCTG                         200

GATTGAGGAA GGCAGAAATG GAGATTCAAA CACCACGTCT                         240

TCTATTATTT TATTAATCAA TCTGTAGACA TGTGTCCCCA                         280

CTGCAGGGAG TGAACTGCTC CAAGGGAGAA ACTTCTGGGA                         320

GCCTCCAAAC TCCTAGCTGT CTCATCCCTT GCCCTGGAGA                         360

GACGGCAGAA CC ATG GCA TTT TAT AGC TGC TGC TGG                       396
              Met Ala Phe Tyr Ser Cys Cys Trp
                1               5

GTC CTC TTG GCA CTC ACC TGG CAC ACC TCT GCC TAC                     432
Val Leu Leu Ala Leu Thr Trp His Thr Ser Ala Tyr
     10                  15                  20

GGG CCA GAC CAG CGA GCC CAA AAG AAG GGG GAC ATT                     468
Gly Pro Asp Gln Arg Ala Gln Lys Lys Gly Asp Ile
                 25                  30

ATC CTT GGG GGG CTC TTT CCT ATT CAT TTT GGA GTA                     504
Ile Leu Gly Gly Leu Phe Pro Ile His Phe Gly Val
         35                  40

GCA GCT AAA GAT CAA GAT CTC AAA TCA AGG CCG GAG                     540
Ala Ala Lys Asp Gln Asp Leu Lys Ser Arg Pro Glu
 45                  50                  55

TCT GTG GAA TGT ATC AGG TAT AAT TTC CGT GGG TTT                     576
Ser Val Glu Cys Ile Arg Tyr Asn Phe Arg Gly Phe
             60                  65

CGC TGG TTA CAG GCT ATG ATA TTT GCC ATA GAG GAG                     612
Arg Trp Leu Gln Ala Met Ile Phe Ala Ile Glu Glu
     70                  75                  80

ATA AAC AGC AGC CCA GCC CTT CTT CCC AAC TTG ACG                     648
Ile Asn Ser Ser Pro Ala Leu Leu Pro Asn Leu Thr
                 85                  90

CTG GGA TAC AGG ATA TTT GAC ACT TGC AAC ACC GTT                     684
Leu Gly Tyr Arg Ile Phe Asp Thr Cys Asn Thr Val
         95                  100

TCT AAG GCC TTG GAA GCC ACC CTG AGT TTT GTT GCT                     720
Ser Lys Ala Leu Glu Ala Thr Leu Ser Phe Val Ala
105                 110                 115
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CAA AAC AAA ATT GAT TCT TTG AAC CTT GAT GAG TTC                    756
Gln Asn Lys Ile Asp Ser Leu Asn Leu Asp Glu Phe
            120                 125

TGC AAC TGC TCA GAG CAC ATT CCC TCT ACG ATT GCT                    792
Cys Asn Cys Ser Glu His Ile Pro Ser Thr Ile Ala
    130                 135                 140

GTG GTG GGA GCA ACT GGC TCA GGC GTC TCC ACG GCA                    828
Val Val Gly Ala Thr Gly Ser Gly Val Ser Thr Ala
                145                 150

GTG GCA AAT CTG CTG GGG CTC TTC TAC ATT CCC CAG                    864
Val Ala Asn Leu Leu Gly Leu Phe Tyr Ile Pro Gln
        155                 160

GTC AGT TAT GCC TCC TCC AGC AGA CTC CTC AGC AAC                    900
Val Ser Tyr Ala Ser Ser Ser Arg Leu Leu Ser Asn
165                 170                 175

AAG AAT CAA TTC AAG TCT TTC CTC CGA ACC ATC CCC                    936
Lys Asn Gln Phe Lys Ser Phe Leu Arg Thr Ile Pro
            180                 185

AAT GAT GAG CAC CAG GCC ACT GCC ATG GCA GAC ATC                    972
Asn Asp Glu His Gln Ala Thr Ala Met Ala Asp Ile
    190                 195                 200

ATC GAG TAT TTC CGC TGG AAC TGG GTG GGC ACA ATT                   1008
Ile Glu Tyr Phe Arg Trp Asn Trp Val Gly Thr Ile
                205                 210

GCA GCT GAT GAC GAC TAT GGG CGG CCG GGG ATT GAG                   1044
Ala Ala Asp Asp Asp Tyr Gly Arg Pro Gly Ile Glu
        215                 220

AAA TTC CGA GAG GAA GCT GAG GAA AGG GAT ATC TGC                   1080
Lys Phe Arg Glu Glu Ala Glu Glu Arg Asp Ile Cys
225                 230                 235

ATC GAC TTC AGT GAA CTC ATC TCC CAG TAC TCT GAT                   1116
Ile Asp Phe Ser Glu Leu Ile Ser Gln Tyr Ser Asp
            240                 245

GAG GAA GAG ATC CAG CAT GTG GTA GAG GTG ATT CAA                   1152
Glu Glu Glu Ile Gln His Val Val Glu Val Ile Gln
    250                 255                 260

AAT TCC ACG GCC AAA GTC ATC GTG GTT TTC TCC AGT                   1188
Asn Ser Thr Ala Lys Val Ile Val Val Phe Ser Ser
                265                 270

GGC CCA GAT CTT GAG CCC CTC ATC AAG GAG ATT GTC                   1224
Gly Pro Asp Leu Glu Pro Leu Ile Lys Glu Ile Val
        275                 280
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CGG CGC AAT ATC ACG GGC AAG ATC TGG CTG GCC AGC          1260
Arg Arg Asn Ile Thr Gly Lys Ile Trp Leu Ala Ser
285                 290                 295

GAG GCC TGG GCC AGC TCC TCC CTG ATC GCC ATG CCT          1296
Glu Ala Trp Ala Ser Ser Ser Leu Ile Ala Met Pro
            300                 305

CAG TAC TTC CAC GTG GTT GGC GGC ACC ATT GGA TTC          1332
Gln Tyr Phe His Val Val Gly Gly Thr Ile Gly Phe
    310                 315                 320

GCT CTG AAG GCT GGG CAG ATC CCA GGC TTC CGG GAA          1368
Ala Leu Lys Ala Gly Gln Ile Pro Gly Phe Arg Glu
                325                 330

TTC CTG AAG AAG GTC CAT CCC AGG AAG TCT GTC CAC          1404
Phe Leu Lys Lys Val His Pro Arg Lys Ser Val His
        335                 340

AAT GGT TTT GCC AAG GAG TTT TGG GAA GAA ACA TTT          1440
Asn Gly Phe Ala Lys Glu Phe Trp Glu Glu Thr Phe
345                 350                 355

AAC TGC CAC CTC CAA GAA GGT GCA AAA GGA CCT TTA          1476
Asn Cys His Leu Gln Glu Gly Ala Lys Gly Pro Leu
            360                 365

CCT GTG GAC ACC TTT CTG AGA GGT CAC GAA GAA AGT          1512
Pro Val Asp Thr Phe Leu Arg Gly His Glu Glu Ser
    370                 375                 380

GGC GAC AGG TTT AGC AAC AGC TCG ACA GCC TTC CGA          1548
Gly Asp Arg Phe Ser Asn Ser Ser Thr Ala Phe Arg
                385                 390

CCC CTC TGT ACA GGG GAT GAG AAC ATC AGC AGT GTC          1584
Pro Leu Cys Thr Gly Asp Glu Asn Ile Ser Ser Val
        395                 400

GAG ACC CCT TAC ATA GAT TAC ACG CAT TTA CGG ATA          1620
Glu Thr Pro Tyr Ile Asp Tyr Thr His Leu Arg Ile
405                 410                 415

TCC TAC AAT GTG TAC TTA GCA GTC TAC TCC ATT GCC          1656
Ser Tyr Asn Val Tyr Leu Ala Val Tyr Ser Ile Ala
            420                 425

CAC GCC TTG CAA GAT ATA TAT ACC TGC TTA CCT GGG          1692
His Ala Leu Gln Asp Ile Tyr Thr Cys Leu Pro Gly
    430                 435                 440

AGA GGG CTC TTC ACC AAT GGC TCC TGT GCA GAC ATC          1728
Arg Gly Leu Phe Thr Asn Gly Ser Cys Ala Asp Ile
                445                 450
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AAG AAA GTT GAG GCG TGG CAG GTC CTG AAG CAC CTA      1764
Lys Lys Val Glu Ala Trp Gln Val Leu Lys His Leu
        455                 460

CGG CAT CTA AAC TTT ACA AAC AAT ATG GGG GAG CAG      1800
Arg His Leu Asn Phe Thr Asn Asn Met Gly Glu Gln
465                 470                 475

GTG ACC TTT GAT GAG TGT GGT GAC CTG GTG GGG AAC      1836
Val Thr Phe Asp Glu Cys Gly Asp Leu Val Gly Asn
            480                 485

TAT TCC ATC ATC AAC TGG CAC CTC TCC CCA GAG GAT      1872
Tyr Ser Ile Ile Asn Trp His Leu Ser Pro Glu Asp
    490                 495                 500

GGC TCC ATC GTG TTT AAG GAA GTC GGG TAT TAC AAC      1908
Gly Ser Ile Val Phe Lys Glu Val Gly Tyr Tyr Asn
                505                 510

GTC TAT GCC AAG AAG GGA GAA AGA CTC TTC ATC AAC      1944
Val Tyr Ala Lys Lys Gly Glu Arg Leu Phe Ile Asn
        515                 520

GAG GAG AAA ATC CTG TGG AGT GGG TTC TCC AGG GAG      1980
Glu Glu Lys Ile Leu Trp Ser Gly Phe Ser Arg Glu
525                 530                 535

GTG CCC TTC TCC AAC TGC AGC CGA GAC TGC CTG GCA      2016
Val Pro Phe Ser Asn Cys Ser Arg Asp Cys Leu Ala
            540                 545

GGG ACC AGG AAA GGG ATC ATT GAG GGG GAG CCC ACC      2052
Gly Thr Arg Lys Gly Ile Ile Glu Gly Glu Pro Thr
    550                 555                 560

TGC TGC TTT GAG TGT GTG GAG TGT CCT GAT GGG GAG      2088
Cys Cys Phe Glu Cys Val Glu Cys Pro Asp Gly Glu
                565                 570

TAT AGT GAT GAG ACA GAT GCC AGT GCC TGT AAC AAG      2124
Tyr Ser Asp Glu Thr Asp Ala Ser Ala Cys Asn Lys
        575                 580

TGC CCA GAT GAC TTC TGG TCC AAT GAG AAC CAC ACC      2160
Cys Pro Asp Asp Phe Trp Ser Asn Glu Asn His Thr
585                 590                 595

TCC TGC ATT GCC AAG GAG ATC GAG TTT CTG TCG TGG      2196
Ser Cys Ile Ala Lys Glu Ile Glu Phe Leu Ser Trp
            600                 605

ACG GAG CCC TTT GGG ATC GCA CTC ACC CTC TTT GCC      2232
Thr Glu Pro Phe Gly Ile Ala Leu Thr Leu Phe Ala
    610                 615                 620
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GTG CTG GGC ATT TTC CTG ACA GCC TTT GTG CTG GGT      2268
Val Leu Gly Ile Phe Leu Thr Ala Phe Val Leu Gly
                625                 630

GTG TTT ATC AAG TTC CGC AAC ACA CCC ATT GTC AAG      2304
Val Phe Ile Lys Phe Arg Asn Thr Pro Ile Val Lys
        635                 640

GCC ACC AAC CGA GAG CTC TCC TAC CTC CTC CTC TTC      2340
Ala Thr Asn Arg Glu Leu Ser Tyr Leu Leu Leu Phe
645                 650                 655

TCC CTG CTC TGC TGC TTC TCC AGC TCC CTG TTC TTC      2376
Ser Leu Leu Cys Cys Phe Ser Ser Ser Leu Phe Phe
            660                 665

ATC GGG GAG CCC CAG GAC TGG ACG TGC CGC CTG CGC      2412
Ile Gly Glu Pro Gln Asp Trp Thr Cys Arg Leu Arg
    670                 675                 680

CAG CCG GCC TTT GGC ATC AGC TTC GTG CTC TGC ATC      2448
Gln Pro Ala Phe Gly Ile Ser Phe Val Leu Cys Ile
                685                 690

TCA TGC ATC CTG GTG AAA ACC AAC CGT GTC CTC CTG      2484
Ser Cys Ile Leu Val Lys Thr Asn Arg Val Leu Leu
        695                 700

GTG TTT GAG GCC AAG ATC CCC ACC AGC TTC CAC CGC      2520
Val Phe Glu Ala Lys Ile Pro Thr Ser Phe His Arg
705                 710                 715

AAG TGG TGG GGG CTC AAC CTG CAG TTC CTG CTG GTT      2556
Lys Trp Trp Gly Leu Asn Leu Gln Phe Leu Leu Val
            720                 725

TTC CTC TGC ACC TTC ATG CAG ATT GTC ATC TGT GTG      2592
Phe Leu Cys Thr Phe Met Gln Ile Val Ile Cys Val
    730                 735                 740

ATC TGG CTC TAC ACC GCG CCC CCC TCA AGC TAC CGC      2628
Ile Trp Leu Tyr Thr Ala Pro Pro Ser Ser Tyr Arg
                745                 750

AAC CAG GAG CTG GAG GAT GAG ATC ATC TTC ATC ACG      2664
Asn Gln Glu Leu Glu Asp Glu Ile Ile Phe Ile Thr
        755                 760

TGC CAC GAG GGC TCC CTC ATG GCC CTG GGC TTC CTG      2700
Cys His Glu Gly Ser Leu Met Ala Leu Gly Phe Leu
765                 770                 775

ATC GGC TAC ACC TGC CTG CTG GCT GCC ATC TGC TTC      2736
Ile Gly Tyr Thr Cys Leu Leu Ala Ala Ile Cys Phe
            780                 785
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TTC TTT GCC TTC AAG TCC CGG AAG CTG CCG GAG AAC      2772
Phe Phe Ala Phe Lys Ser Arg Lys Leu Pro Glu Asn
    790                 795                 800

TTC AAT GAA GCC AAG TTC ATC ACC TTC AGC ATG CTC      2808
Phe Asn Glu Ala Lys Phe Ile Thr Phe Ser Met Leu
                805                 810

ATC TTC TTC ATC GTC TGG ATC TCC TTC ATT CCA GCC      2844
Ile Phe Phe Ile Val Trp Ile Ser Phe Ile Pro Ala
        815                 820

TAT GCC AGC ACC TAT GGC AAG TTT GTC TCT GCC GTA      2880
Tyr Ala Ser Thr Tyr Gly Lys Phe Val Ser Ala Val
825                 830                 835

GAG GTG ATT GCC ATC CTG GCA GCC AGC TTT GGC TTG      2916
Glu Val Ile Ala Ile Leu Ala Ala Ser Phe Gly Leu
            840                 845

CTG GCG TGC ATC TTC TTC AAC AAG ATC TAC ATC ATT      2952
Leu Ala Cys Ile Phe Phe Asn Lys Ile Tyr Ile Ile
    850                 855                 860

CTC TTC AAG CCA TCC CGC AAC ACC ATC GAG GAG GTG      2988
Leu Phe Lys Pro Ser Arg Asn Thr Ile Glu Glu Val
                865                 870

CGT TGC AGC ACC GCA GCT CAC GCT TTC AAG GTG GCT      3024
Arg Cys Ser Thr Ala Ala His Ala Phe Lys Val Ala
        875                 880

GCC CGG GCC ACG CTG CGC CGC AGC AAC GTC TCC CGC      3060
Ala Arg Ala Thr Leu Arg Arg Ser Asn Val Ser Arg
885                 890                 895

AAG CGG TCC AGC AGC CTT GGA GGC TCC ACG GGA TCC      3096
Lys Arg Ser Ser Ser Leu Gly Gly Ser Thr Gly Ser
            900                 905

ACC CCC TCC TCC TCC ATC AGC AGC AAG AGC AAC AGC      3132
Thr Pro Ser Ser Ser Ile Ser Ser Lys Ser Asn Ser
    910                 915                 920

GAA GAC CCA TTC CCA CAG CCC GAG AGG CAG AAG CAG      3168
Glu Asp Pro Phe Pro Gln Pro Glu Arg Gln Lys Gln
                925                 930

CAG CAG CCG CTG GCC CTA ACC CAG CAA GAG CAG CAG      3204
Gln Gln Pro Leu Ala Leu Thr Gln Gln Glu Gln Gln
        935                 940

CAG CAG CCC CTG ACC CTC CCA CAG CAG CAA CGA TCT      3240
Gln Gln Pro Leu Thr Leu Pro Gln Gln Gln Arg Ser
945                 950                 955
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CAG CAG CAG CCC AGA TGC AAG CAG AAG GTC ATC TTT                    3276
Gln Gln Gln Pro Arg Cys Lys Gln Lys Val Ile Phe
            960                 965

GGC AGC GGC ACG GTC ACC TTC TCA CTG AGC TTT GAT                    3312
Gly Ser Gly Thr Val Thr Phe Ser Leu Ser Phe Asp
    970                 975                 980

GAG CCT CAG AAG AAC GCC ATG GCC CAC GGG AAT TCT                    3348
Glu Pro Gln Lys Asn Ala Met Ala His Gly Asn Ser
                985                 990

ACG CAC CAG AAC TCC CTG GAG GCC CAG AAA AGC AGC                    3384
Thr His Gln Asn Ser Leu Glu Ala Gln Lys Ser Ser
        995                 1000

GAT ACG CTG ACC CGA CAC CAG CCA TTA CTC CCG CTG                    3420
Asp Thr Leu Thr Arg His Gln Pro Leu Leu Pro Leu
1005                1010                1015

CAG TGC GGG GAA ACG GAC TTA GAT CTG ACC GTC CAG                    3456
Gln Cys Gly Glu Thr Asp Leu Asp Leu Thr Val Gln
            1020                1025

GAA ACA GGT CTG CAA GGA CCT GTG GGT GGA GAC CAG                    3492
Glu Thr Gly Leu Gln Gly Pro Val Gly Gly Asp Gln
    1030                1035                1040

CGG CCA GAG GTG GAG GAC CCT GAA GAG TTG TCC CCA                    3528
Arg Pro Glu Val Glu Asp Pro Glu Glu Leu Ser Pro
                1045                1050

GCA CTT GTA GTG TCC AGT TCA CAG AGC TTT GTC ATC                    3564
Ala Leu Val Val Ser Ser Ser Gln Ser Phe Val Ile
        1055                1060

AGT GGT GGA GGC AGC ACT GTT ACA GAA AAC GTA GTG                    3600
Ser Gly Gly Gly Ser Thr Val Thr Glu Asn Val Val
1065                1070                1075

AAT TCA TAAAATGGAA GGAGAAGACT GGGCTAGGGA                           3636
Asn Ser

GAATGCAGAG AGGTTTCTTG GGGTCCCAGG GATGAGGAAT                        3676

CGCCCCAGAC TCCTTTCCTC TGAGGAAGAA GGGATAATAG                        3716

ACACATCAAA TGCCCCGAAT TTAGTCACAC CATCTTAAAT                        3756

GACAGTGAAT TGACCCATGT TCCCTTTAAA AAAAAAAAAA                        3796

AAAAAGCGGC CGC                                                    3809
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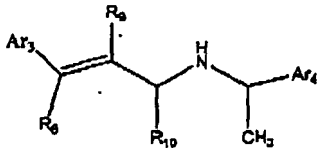
Claims

1. A compound for use as a medicament having the formula:

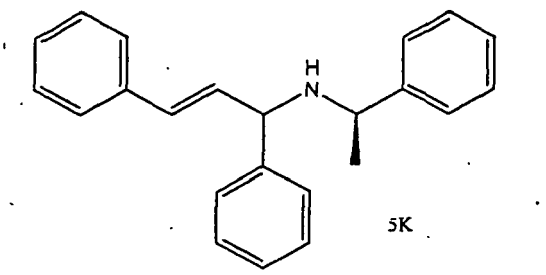


wherein Ar_3 is phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of: C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, benzyl, benzyloxy, dimethylbenzyl. NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acetyl, and ethylene dioxy;
Ar_4 is phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, and acetoxy;
R_8 is either hydrogen or phenyl;
R_9 is either hydrogen or methyl; and
R_{10} is either hydrogen, methyl, or phenyl;
or a pharmaceutically acceptable salt or complex thereof.

2. The compound of claim 1, wherein Ar_3 is phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, benzyl, benzyloxy, dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acetyl, and ethylenedioxy;
Ar_4 is phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of: C_{1-4} alkyl, halogen C_{1-4} alkoxy, C_{1-4} thioalkyl, methylenedioxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, CH_2OH, $CONH_2$, CN, and acetoxy.

3. The compound of claim 2 wherein Ar_3 is phenyl optionally substituted with 0 to 5 substituents, each independently selected from the group consisting of: C_{1-4} alkyl of 1 to 3 carbon atoms, halogen, C_{1-4} alkoxy of 1 to 3 carbon atoms, C_{1-4} thioalkyl of 1 to 3 carbon atoms, methylenedioxy, C_{1-4} haloalkyl of 1 to 3 carbon atoms, C_{1-4} haloalkoxy of 1 to 3 carbon atoms, OH, CH_2OH, $CONH_2$, CN, acetoxy, benzyl, benzyloxy, dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acetyl, and ethylenedioxy; and
Ar_4 is phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of: C_{1-4} alkyl of 1 to 3 carbon atoms, halogen, C_{1-4} alkoxy of 1 to 3 carbon atoms, C_{1-4} thioalkyl of 1 to 3 carbon atoms, methylenedioxy, C_{1-4} haloalkyl of 1 to 3 carbon atoms, C_{1-4} haloalkoxy of 1 to 3 carbon atoms, OH, CH_2OH, $CONH_2$, CN and acetoxy.

4. A compound for use as a medicament having a formula selected from the group



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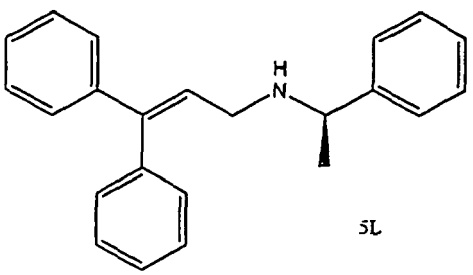

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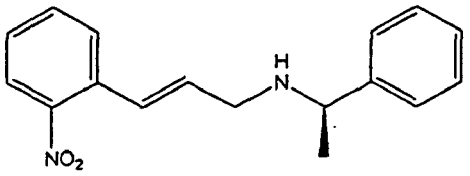
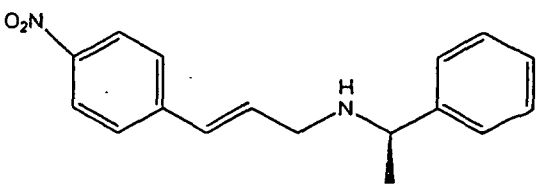
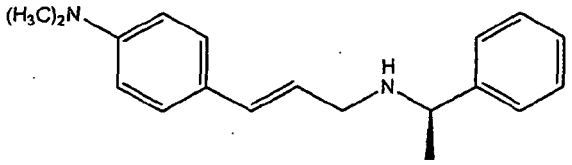


5M



5N



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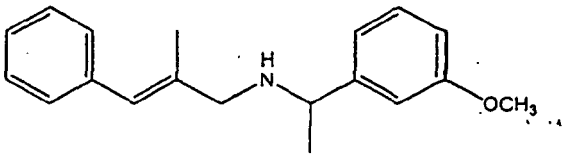
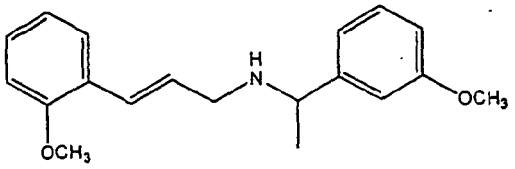
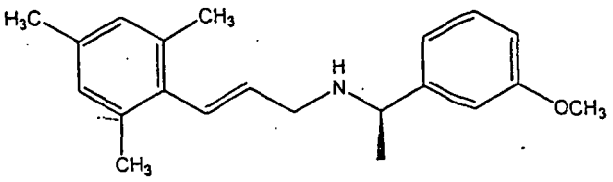


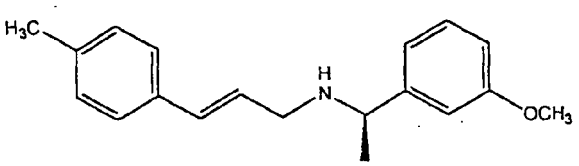
6D



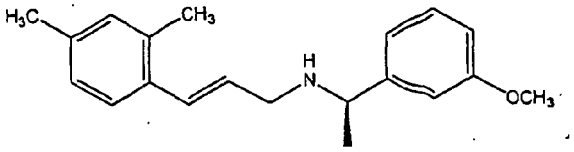
8T



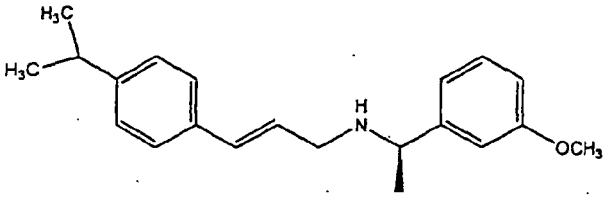
12D



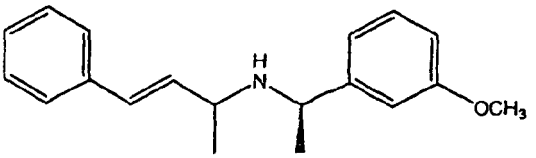
12B



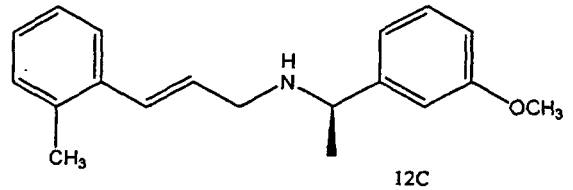
12F



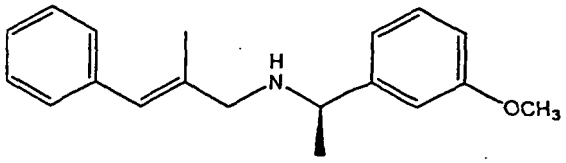
12E



25H



12C



25G

5. Compound number 12C ((R)-N-[3-(2-methylphenyl)prop-2-enyl]prop2-enyl]-1-(3-methoxyphenyl)ethylamine or a pharmaceutically acceptable salt or complex thereof, for use as a medicament.

6. Compound 12D ((R)-N-[3-(2,4,6-trimethylphenyl)prop-2-enyl] 1-(3methoxyphenyl)ethylamine or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

7. Compound 12E (R)-[3-(4-isopropylphenyl)prop-2-enyl]-1-(3-methoxyphenyl) ethylamine or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

8. Compound 12F ((R)-N-(3-(2,4-dimethylphenyl)prop-2-enyl]-1-(3-methoxyphenyl) ethylamine or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

9. Compound 12G ((R)-N-[3-(3-methylphenyl)prop-2-enyl]-1-(3-methoxyphenyl) ethylamine or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

10. Compound 25E ((R-N-(3-phenylprop-2-en-1-yl)-1-(3-mothoxyphenyl) ethylamine; or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

11. Compound 25G (R)-N-(2-methyl-3-phenylprop-2-enyl)-1-(3-methoxypheayl) ethylamine or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

12. Compound 25H ((R,R)-N-(2-methyl-4-phenylbut-3-enyl)-1-(3-methoxyphenyl) ethylamine or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

13. Compound 25I (S,R)-N-(2-methyl-4-phenybut-3-enyl)-1-(3-methoxyphenyl) ethylamine-or a pharmaceutically acceptable salt or complex thereof for use as a medicament.

14. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any of claims 1-13.

15. Use of the compound of any of claims 1-13 for the preparation of a medicament for treating a patient having a disease or disorder **characterized by** abnormal bone and mineral homeostasis.

16. Use of the compound of any of claims 1-13 for the preparation of a medicament for treating a patient having hyperparathyroidism.

17. Use of the compound of any of claims 1-13 for the preparation of a medicament for treating a patient having Paget's disease.

18. Use of the compound of any of claims 1-13 for the preparation of a medicament for treating a patient having osteoperosis.

19. Use of the compound of any of claims 1-13 for the preparation of a medicament for treating a patient having hypertension.

20. Use of the compound of any of claims 1-13 for the preparation of a medicament for treating a patient having renal osteodystrophy.

21. Use of the compound of any of claims 1-13 for the preparation of a medicament for treating a patient having a hypercalcemic disorder.

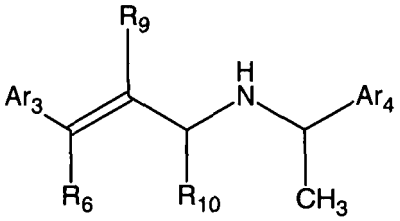
22. Use of compound number 12B ((R)-N-[3-(4-methylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamine or a pharmaceutically acceptable salt or complex thereof for the preparation of a medicament for decreasing parathyroid hormone level in a patient to achieve a beneficial effect.

23. Use of compound number 25E ((R)-N-(3-phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamine or a pharmaceutically acceptable salt or complex thereof for the preparation of a medicament for decreasing parathyroid hormone level in a patient to achieve a beneficial effect.

24. Use of compound number 25E ((R)-N-(3-phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamine or a pharmaceutically acceptable salt or complex thereof for the preparation of a medicament for inhibiting bone resorption in a patient.

Patentansprüche

1. Verbindung zur Verwendung als ein Medikament mit der Formel:

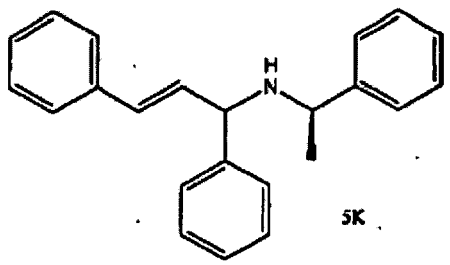


wobei Ar_3 Phenyl ist, welches gegebenenfalls mit 0-5 Substituenten substituiert ist, die jeweils unabhängig ausgewählt sind aus: C_{1-4}-Alkyl, Halogen, C_{1-4}-Alkoxy, C_{1-4}-Thioalkyl, Methylendioxy, C_{1-4}-Halogenalkyl, C_{1-4}-Halogenalkoxy, OH, CH_2OH, $CONH_2$, CN, Acetoxy, Benzyl, Benzyloxy, Dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, Acetyl und Ethylendioxy;
Ar_4 Phenyl ist, welches gegebenenfalls mit 0-5 Substituenten substituiert ist, die jeweils unabhängig ausgewählt sind aus: C_{1-4}-Alkyl, Halogen, C_{1-4}-Alkoxy, C_{1-4}-Thioalkyl, Methylendioxy, C_{1-4}-Halogenalkyl, C_{1-4}-Halogenalkoxy, OH, CH_2OH, $CONH_2$, CN und Acetoxy;
R_8 entweder Wasserstoff oder Phenyl ist;
R_9 entweder Wasserstoff oder Methyl ist; und
R_{10} entweder Wasserstoff, Methyl oder Phenyl ist;
oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon.

2. Verbindung gemäß Anspruch 1, wobei Ar_3 Phenyl ist, welches gegebenenfalls mit 0-5 Substituenten substituiert ist, die jeweils unabhängig ausgewählt sind aus: Halogen, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, C_{1-4}-Thioalkyl, Methylendioxy, C_{1-4}-Halogenalkyl, C_{1-4}-Halogenalkoxy, OH, CH_2OH, $CONH_2$, CN, Acetoxy, Benzyl, Benzyloxy, Dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, Acetyl und Ethylendioxy;
Ar_4 Phenyl ist, welches gegebenenfalls mit 0-5 Substituenten substituiert ist, die jeweils unabhängig ausgewählt sind aus: C_{1-4}-Alkyl, Halogen, C_{1-4}-Alkoxy, C_{1-4}-Thioalkyl, Methylendioxy, C_{1-4}-Halogenalkyl, C_{1-4}-Halogenalkoxy, OH, CH_2OH, $CONH_2$, CN und Acetoxy.

3. Verbindung gemäß Anspruch 2, wobei Ar_3 Phenyl ist, welches gegebenenfalls mit 0-5 Substituenten substituiert ist, die jeweils unabhängig ausgewählt sind aus: C_{1-4}-Alkyl mit 1 bis 3 Kohlenstoffatomen, Halogen, C_{1-4}-Alkoxy mit 1 bis 3 Kohlenstoffatomen, C_{1-4}-Thioalkyl mit 1 bis 3 Kohlenstoffatomen, Methylendioxy, C_{1-4}-Halogenalkyl mit 1 bis 3 Kohlenstoffatomen, C_{1-4}-Halogenalkoxy mit 1 bis 3 Kohlenstoffatomen, OH, CH_2OH, $CONH_2$, CN, Acetoxy, Benzyl, Benzyloxy, Dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, Acetyl und Ethylendioxy; und
Ar_4 Phenyl ist, welches gegebenenfalls mit 0-5 Substituenten substituiert ist, die jeweils unabhängig ausgewählt sind aus: C_{1-4}-Alkyl mit 1 bis 3 Kohlenstoffatomen, Halogen, C_{1-4}-Alkoxy mit 1 bis 3 Kohlenstoffatomen, C_{1-4}-Thioalkyl mit 1 bis 3 Kohlenstoffatomen, Methylendioxy, C_{1-4}-Halogenalkyl mit 1 bis 3 Kohlenstoffatomen, C_{1-4}-Halogenalkoxy mit 1 bis 3 Kohlenstoffatomen, OH, CH_2OH, $CONH_2$, CN und Acetoxy.

4. Verbindung zur Verwendung als ein Medikament mit einer Formel, ausgewählt aus:



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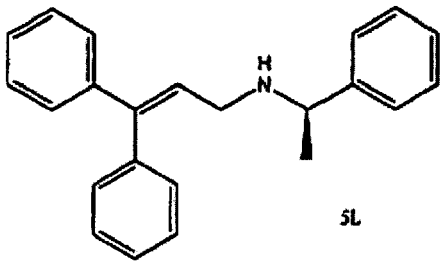
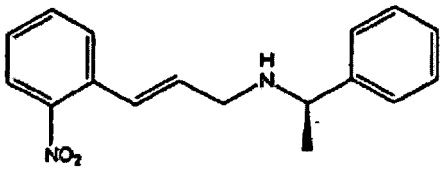
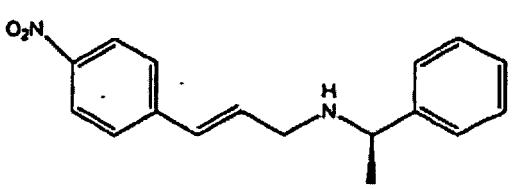


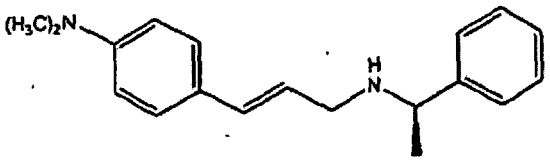
5L



5M



5N



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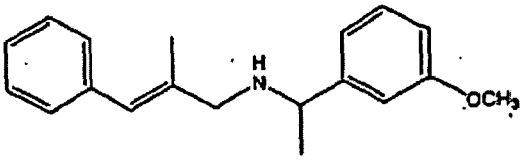
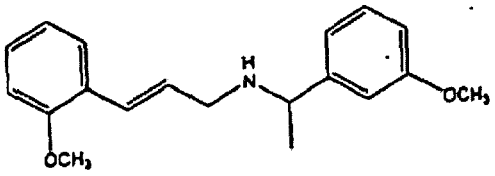
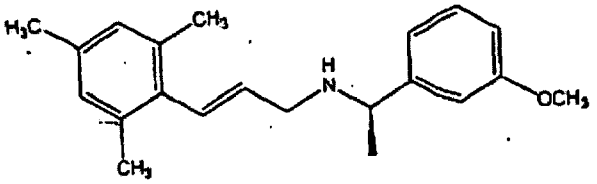


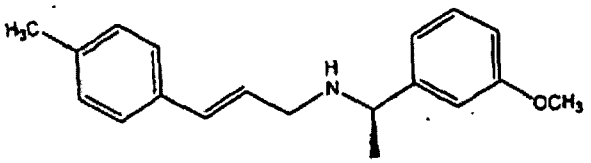
6D



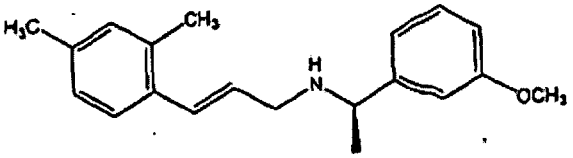
8T



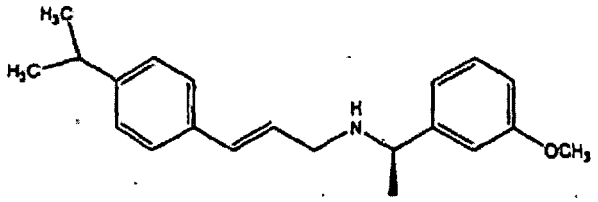
12D



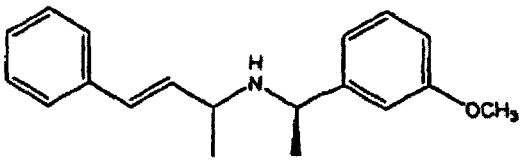
12B



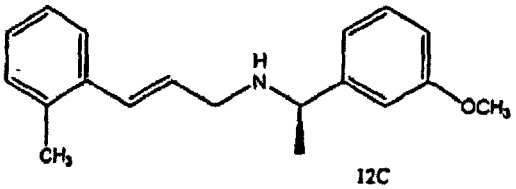
12F



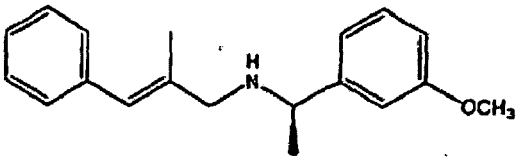
12E



25H



12C



25G

5. Verbindung der Nummer 12C (R)-N-[3-(2-Methylphenyl)prop-2-enyl]prop2-enyl]-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

6. Verbindung 12D (R)-N-[3-(2,4,6-Trimethylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

7. Verbindung 12E (R)-[3-(4-Isopropylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

8. Verbindung 12F (R)-N-[3-(2,4-Dimethylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

9. Verbindung 12G (R)-N-[3-(3-Methylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

10. Verbindung 25E (R)-N-(3-Phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

11. Verbindung 25G (R)-N-(2-Methyl-3-phenylprop-2-enyl)-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

12. Verbindung 25H (R,R)-N-(2-Methyl-4-phenylbut-3-enyl)-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

13. Verbindung 25I (S,R)-N-(2-Methyl-4-phenylbut-3-enyl)-1-(3-methoxyphenyl)ethylamin oder ein pharmazeutisch verträgliches Salz oder ein pharmazeutisch verträglicher Komplex davon zur Verwendung als ein Medikament.

14. Arzneimittel, umfassend eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 13.

15. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Medikaments zur Behandlung eines Patienten mit einer Erkrankung oder Störung, die durch abnormale Knochen- und Mineralhomeostase **gekennzeichnet** ist.

16. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Medikaments zur Behandlung eines Patienten mit Hyperparathyroidismus.

17. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Medikaments zur

Behandlung eines Patienten mit Paget-Syndrom.

18. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Medikaments zur Behandlung eines Patienten mit Osteoporose.

19. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Medikaments zur Behandlung eines Patienten mit Hypertonie.

20. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Medikaments zur Behandlung eines Patienten mit renaler Osteodystrophie.

21. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Medikaments zur Behandlung eines Patienten mit einer hypercalcämischen Störung.

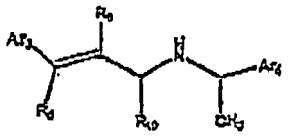
22. Verwendung der Verbindung der Nummer 12B (R)-N-[3-(4-Methylphenyl)prop-2-enyl]-1-(3-methoxyphenyl)ethylamin oder eines pharmazeutisch verträglichen Salzes oder Komplexes davon für die Herstellung eines Medikaments zur Senkung des Parathyreoid-Hormonspiegels in einem Patienten zum Erreichen einer heilsamen Wirkung.

23. Verwendung der Verbindung der Nummer 25E (R)-N-(3-Phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamin oder eines pharmazeutisch verträglichen Salzes oder Komplexes davon für die Herstellung eines Medikaments zur Senkung des Parathyreoid-Hormonspiegels in einem Patienten zum Erreichen einer heilsamen Wirkung.

24. Verwendung der Verbindung der Nummer 25E (R)-N-(3-Phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamin oder eines pharmazeutisch verträglichen Salzes oder Komplexes davon für die Herstellung eines Medikaments zur Verhinderung von Knochenresorption in einem Patienten.

Revendications

1. Composé pour une utilisation comme médicament présentant la formule :

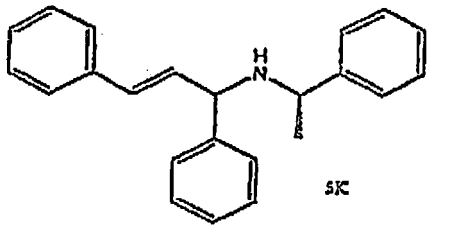


dans laquelle Ar_3 est un phényle éventuellement substitué par 0 à 5 substituants, chacun indépendamment choisi parmi: C_{1-4} alkyle, halogène, C_{1-4} alkoxy, C_{1-4} thioalkyle, méthylènedioxy, C_{1-4} halogénoalkyle, C_{1-4} halogénoalkoxy, OH, CH_2OH, $CONH_2$, CN, acétoxy, benzyle, benzyloxy, diméthylbenzyle, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acétyle et éthylène dioxy ;
Ar_4 est un phényle éventuellement substitué par 0 à 5 substituants, chacun indépendamment choisi parmi : C_{1-4} alkyle, halogène, C_{1-4} alkoxy, C_{1-4} thioalkyle, méthylènedioxy, C_{1-4} halogénoalkyle, C_{1-4} halogénoalkoxy, OH, CH_2OH, $CONH_2$, CN et acétoxy ;
R_8 est hydrogène ou phényle ;
R_9 est hydrogène ou méthyle ; et
R_{10} est hydrogène, méthyle ou phényle ;
ou un de ses sels ou complexes pharmaceutiquement acceptables.

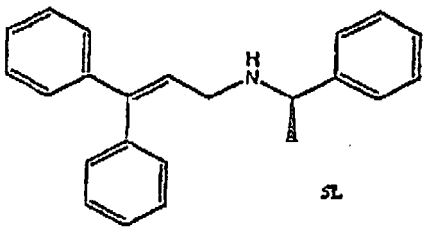
2. Composé selon la revendication 1, dans lequel Ar_3 est un phényle éventuellement substitué par 0 à 5 substituants, chacun indépendamment choisi parmi : halogène, C_{1-4} alkyle, C_{1-4} alkoxy, C_{1-4} thioalkyle, méthylènedioxy, C_{1-4} halogénoalkyle, C_{1-4} halogénoalkoxy, OH, CH_2OH, $CONH_2$, CN, acétoxy, benzyle, benzyloxy, diméthylbenzyle, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acétyle et éthylène dioxy ;
Ar_4 est un phényle éventuellement substitué par 0 à 5 substituants, chacun indépendamment choisi parmi : C_{1-4} alkyle, halogène, C_{1-4} alkoxy, C_{1-4} thioalkyle, méthylènedioxy, C_{1-4} haogénoalkyle, C_{1-4} halogénoalkoxy, OH, CH_2OH, $CONH_2$, CN et acétoxy.

3. Composé selon la revendication 2, dans lequel Ar_3 est un phényle éventuellement substitué par 0 à 5 substituants, chacun indépendamment choisi parmi : C_{1-4} alkyle de 1 à 3 atomes de carbone, halogène, C_{1-4} alkoxy de 1 à 3 atomes de carbone, C_{1-4} thioalkyle de 1 à 3 atomes de carbone, méthylènedioxy, C_{1-4} halogénoalkyle de 1 à 3 atomes de carbone, C_{1-4} halogénoalkoxy de 1 à 3 atomes de carbone, OH, CH_2OH, $CONH_2$, CN, acétoxy, benzyle, benzyloxy, diméthylberl-yle, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acétyle et éthylène dioxy ; et
Ar_4 est un phényle éventuellement substitué par 0 à 5 substituants, chacun indépendamment choisi parmi : C_{1-4} alkyle de 1 à 3 atomes de carbone, halogène, C_{1-4} alkoxy de 1 à 3 atomes de carbone, C_{1-4} thioalkyle de 1 à 3 atomes de carbone, méthylènedioxy, C_{1-4} halogénoalkyle de 1 à 3 atomes de carbone, C_{1-4} halogénoalkoxy de 1 à 3 atomes de carbone, OH, CH_2OH, $CONH_2$, CN et acétoxy.

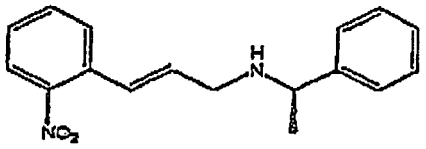
4. Composé pour une utilisation comme médicament présentant une formule choisie parmi:



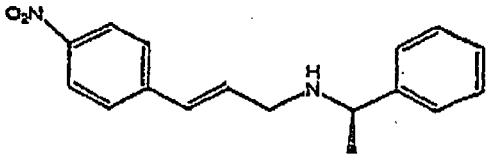
5K



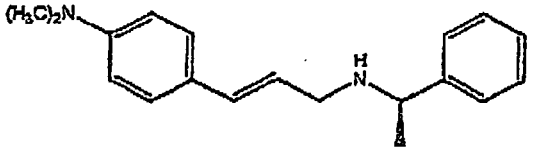
5L



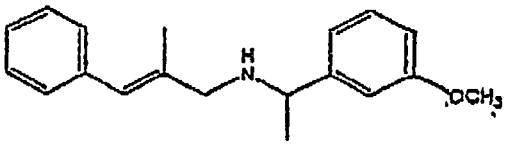
5M



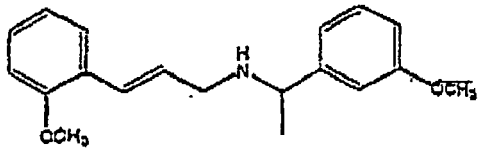
5N



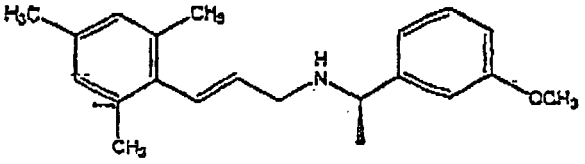
5O



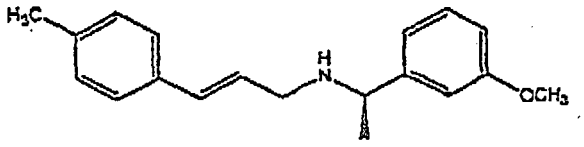
6D



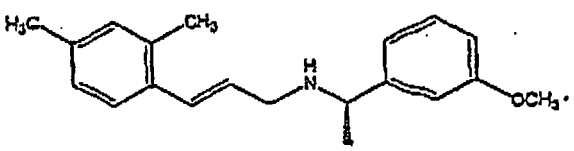
8T



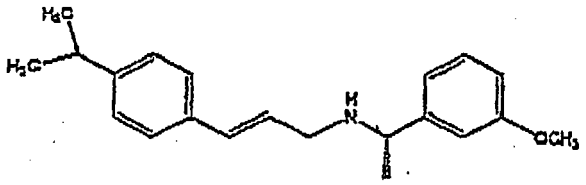
12D



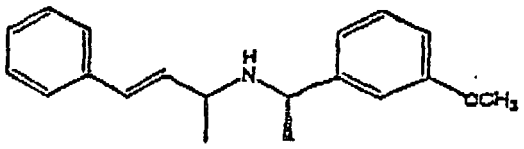
12B



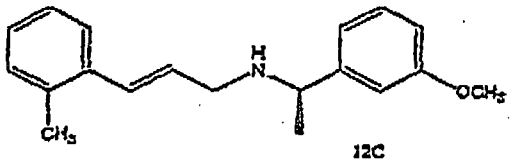
12F



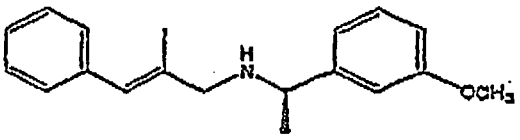
12E



25H



12C



25G

5. Composé numéro 12C (R)-N-[3-(2-méthylphényl)prop-2-ényl]prop-2-ényl]-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

6. Composé numéro 12D (R)-N-[3-(2,4,6-triméthylphényl)prop-2-ényl]-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

7. Composé numéro 12E (R)-[3-(4-isopropylphényl)prop-2-ényl]-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

8. Composé numéro 12F (R)-N-[3-(2,4-diméthylphényl)prop-2-ényl]-1-(3-méthoxyphényl)éthylarnine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

9. Compose numéro 12G (R)-N-[3-(3-méthylphényl)prop-2-ényl]-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

10. Composé numéro 25E (R)-N-(3-phénylprop-2-en-1-yl)-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

11. Composé numéro 25G (R)-N-(2-méthyl-3-phénylprop-2-ényl)-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

12. Composé numéro 25H (R,R)-N-(2-méthyl-4-phénylbut-3-ényl)-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

13. Composé numéro 25I (S,R)-N-(2-méthyl-4-phénylbut-3-ényl)-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables, pour une utilisation comme médicament.

14. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé selon l'une des

revendications 1-13.

15. Utilisation d'un composé selon l'une des revendications 1-13 pour la préparation d'un médicament destiné à traiter un patient ayant une maladie ou un désordre **caractérisé par** une homéostasie osseuse ou minérale anormale.

16. Utilisation d'un composé selon l'une des revendications 1-13 pour la préparation d'un médicament destiné à traiter un patient ayant une hyperparathyroïdie.

17. Utilisation d'un composé selon l'une des revendications 1-13 pour la préparation d'un médicament destiné à traiter un patient ayant la maladie de Paget.

18. Utilisation d'un composé selon l'une des revendications 1-13 pour la préparation d'un médicament destiné à traiter un patient ayant une ostéoporose.

19. Utilisation d'un composé selon l'une des revendications 1-13 pour la préparation d'un médicament destiné à traiter un patient ayant de l'hypertension.

20. Utilisation d'un composé selon l'une des revendications 1-13 pour la préparation d'un médicament destiné à traiter un patient ayant une ostéodystrophie rénale.

21. Utilisation d'un composé selon l'une des revendications 1-13 pour la préparation d'un médicament destiné à traiter un patient ayant un désordre hypercalcémique.

22. Utilisation du composé numéro 12B (R)-N-[3-(4-méthylphényl)prop-2-ényl]-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables pour la préparation d'un médicament destiné à diminuer le taux d'hormones parathyroïdiennes chez un patient pour obtenir un effet bénéfique.

23. Utilisation du composé numéro 25E (R)-N-(3-phénylprop-2-én-1-yl)-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables pour la préparation d'un médicament destiné à diminuer le taux d'hormones parathyroïdiennes chez un patient pour obtenir un effet bénéfique.

24. Utilisation du composé numéro 25E (R)-N-(3-phénylprop-2-én-1-yl)-1-(3-méthoxyphényl)éthylamine ou un de ses sels ou complexes pharmaceutiquement acceptables pour la préparation d'un médicament destiné à inhiber la résorption osseuse chez un patient.

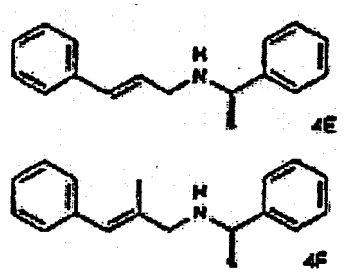


FIG. 1c

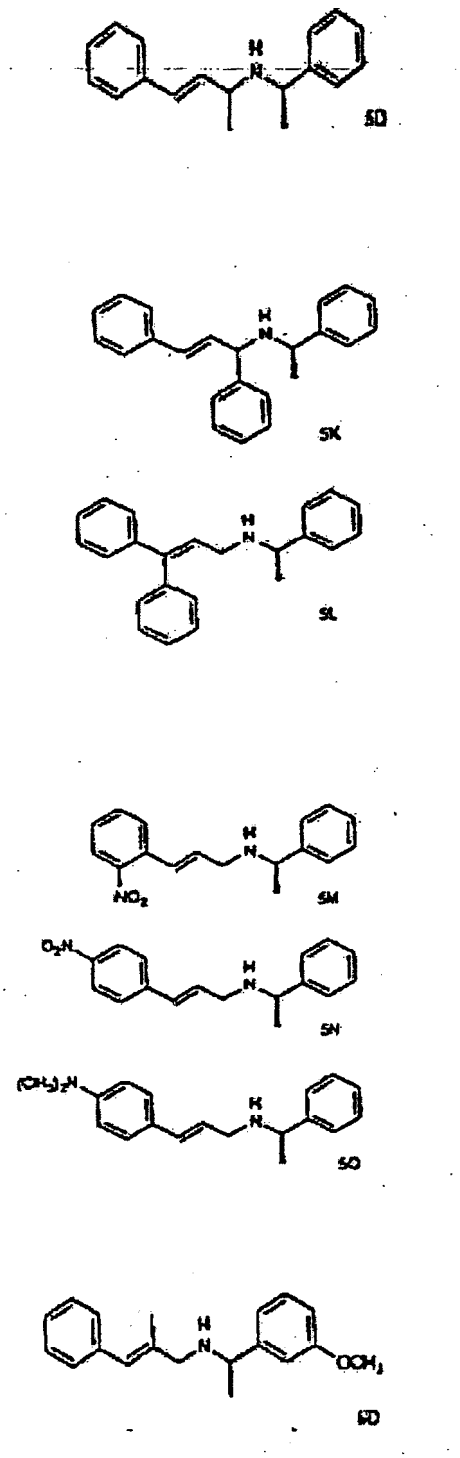


FIG. 1d

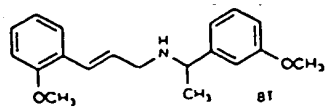


FIG. 1f.

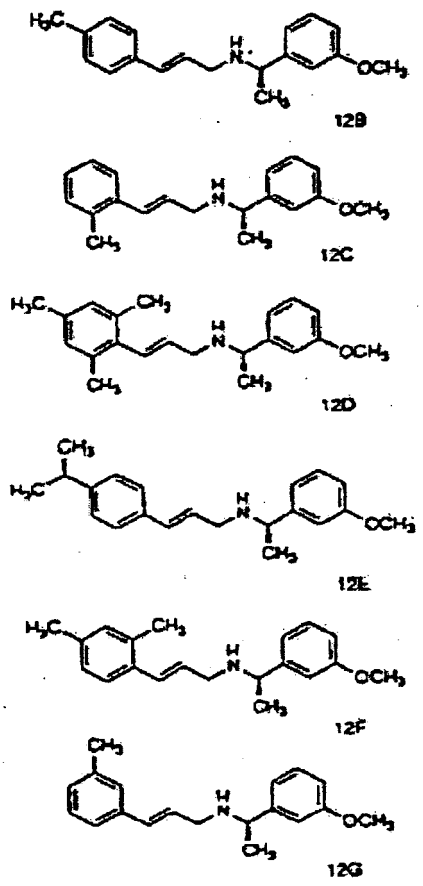


FIG. 1h

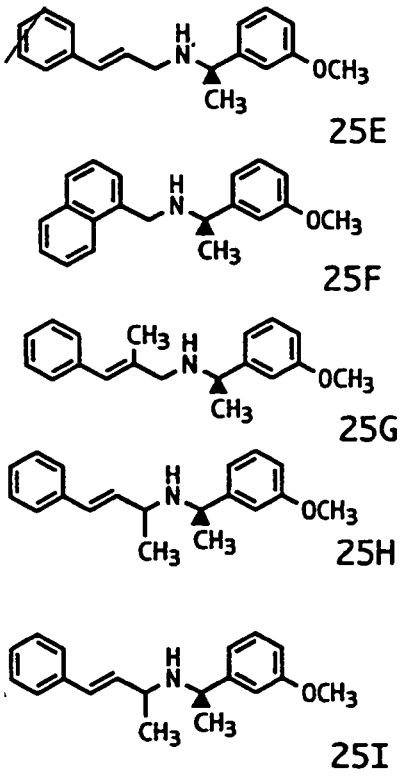

H
N
OCH3
CH3
25E
H
N
OCH3
CH3
25F
CH3
H
N
OCH3
CH3
25G
H
N
OCH3
CH3
CH3
25H
H
N
OCH3
CH3
CH3
25I

FIG. 1q.

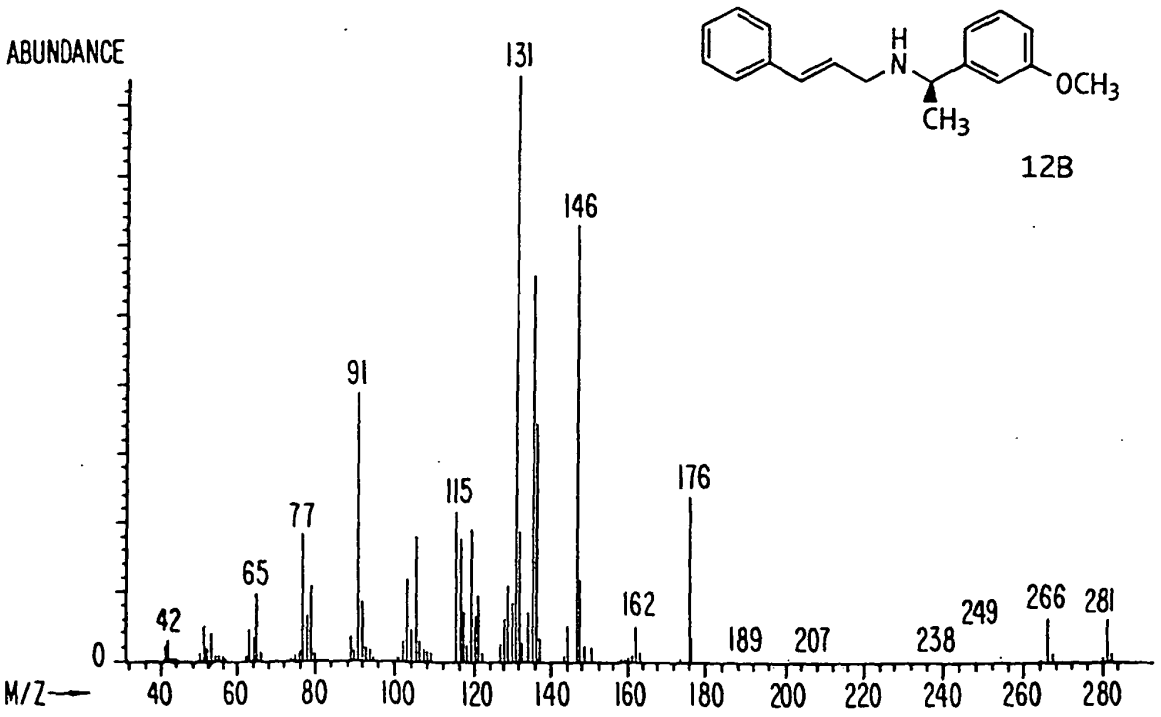
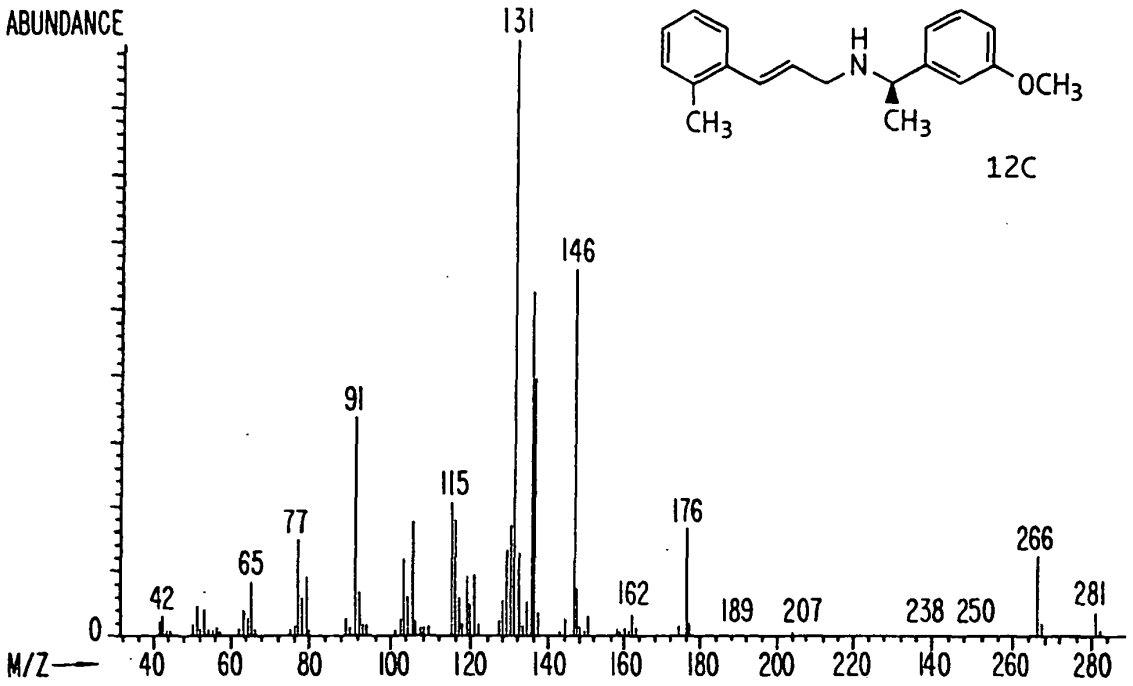

ABUNDANCE
131
146
91
115
77
65
42
176
162
189
207
238
249
266
281
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
H
N
OCH3
CH3
12B

FIG. 30.


ABUNDANCE
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146
91
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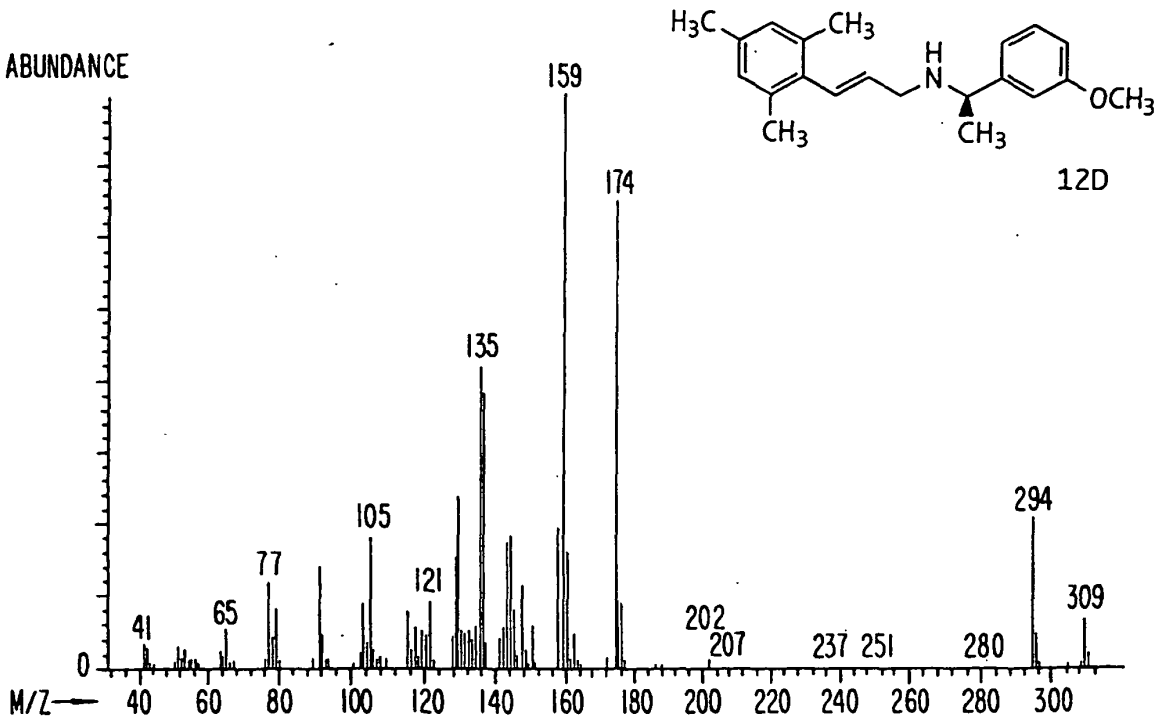
207
238
250
266
281
0
M/Z
40
60
80
100
120
140
160
180
200
220
140
260
280
H
N
CH3
CH3
OCH3
12C

FIG. 31.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237
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309
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M/Z
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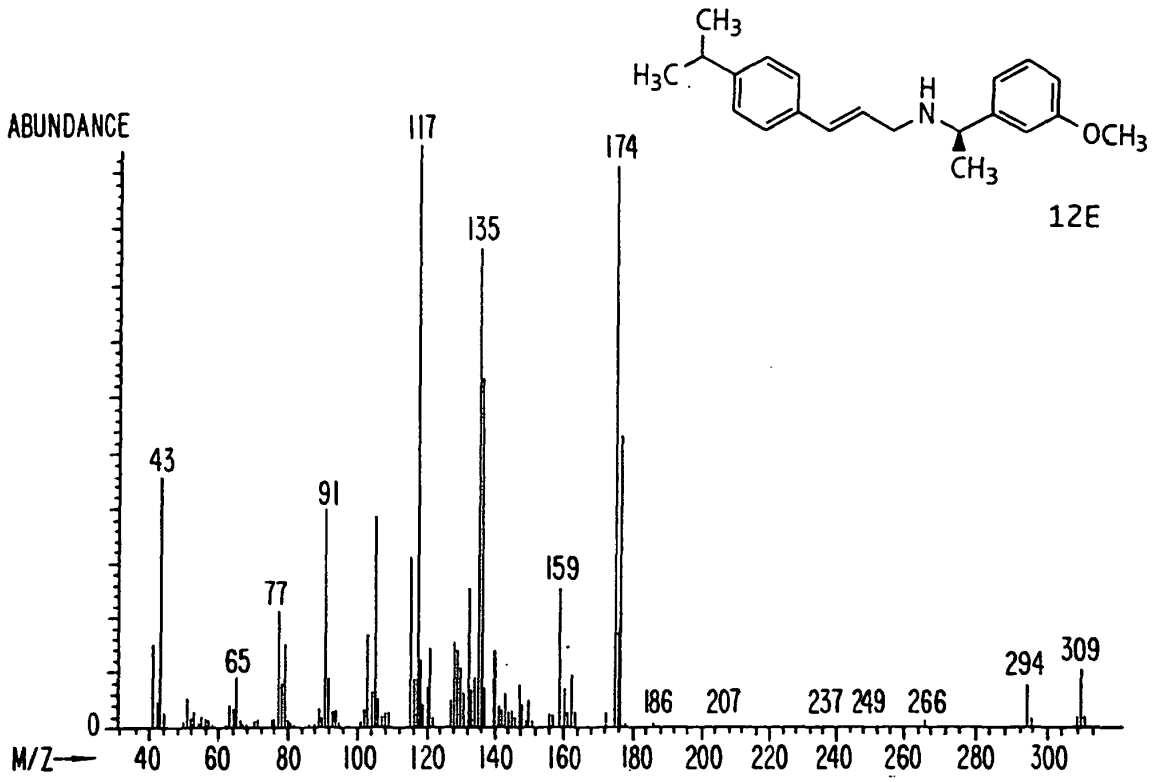
60
80
100
120
140
160
180
200
220
240
260
280
300
H3C
CH3
CH3
H
N
CH3
OCH3
12D

FIG. 32.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43
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159
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294
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186
207
237 249 266
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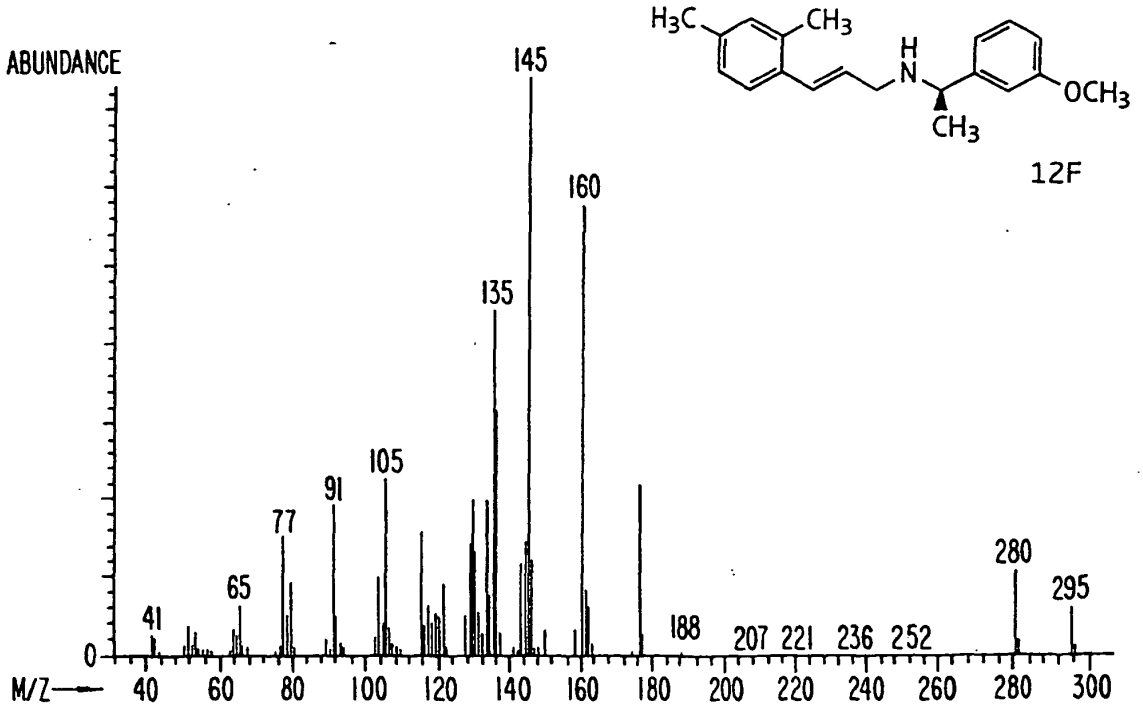
CH3
H3C
H
N
OCH3
CH3
12E

FIG. 33.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91
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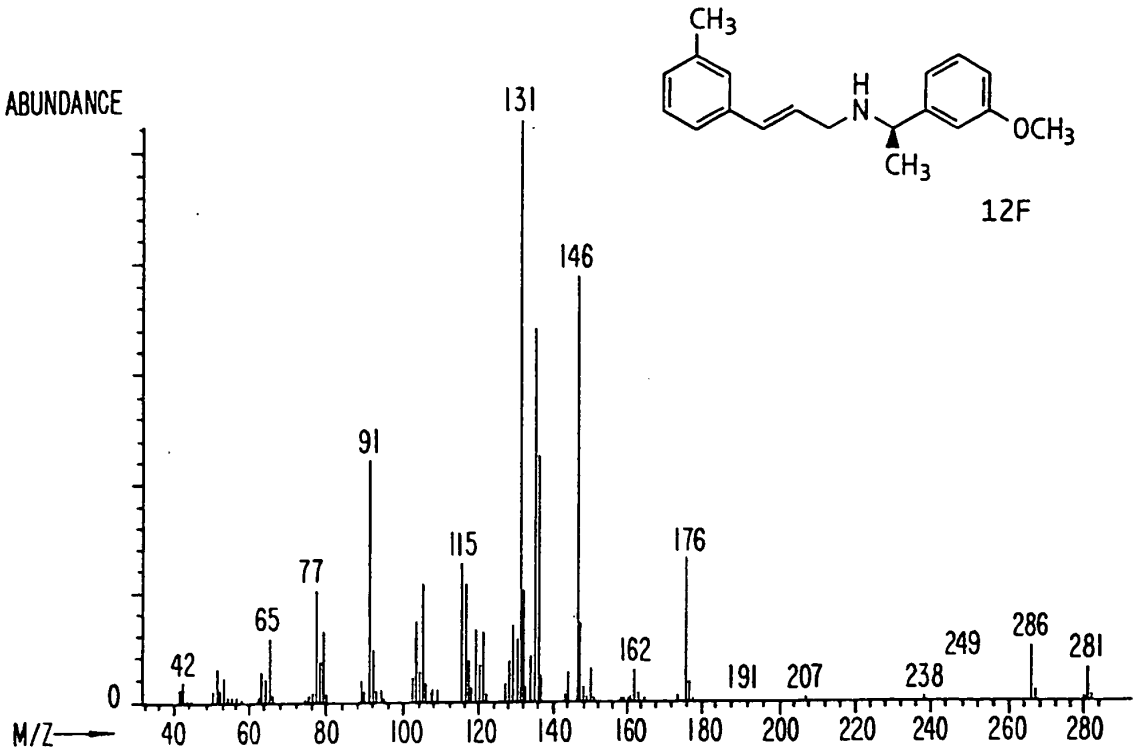
295
188
207 221 236 252
0
M/Z
40 60 80 100 120 140 160 180 200 220 240 260 280 300
H3C
CH3
H
N
OCH3
CH3
12F

FIG. 34.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238
249
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281
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M/Z
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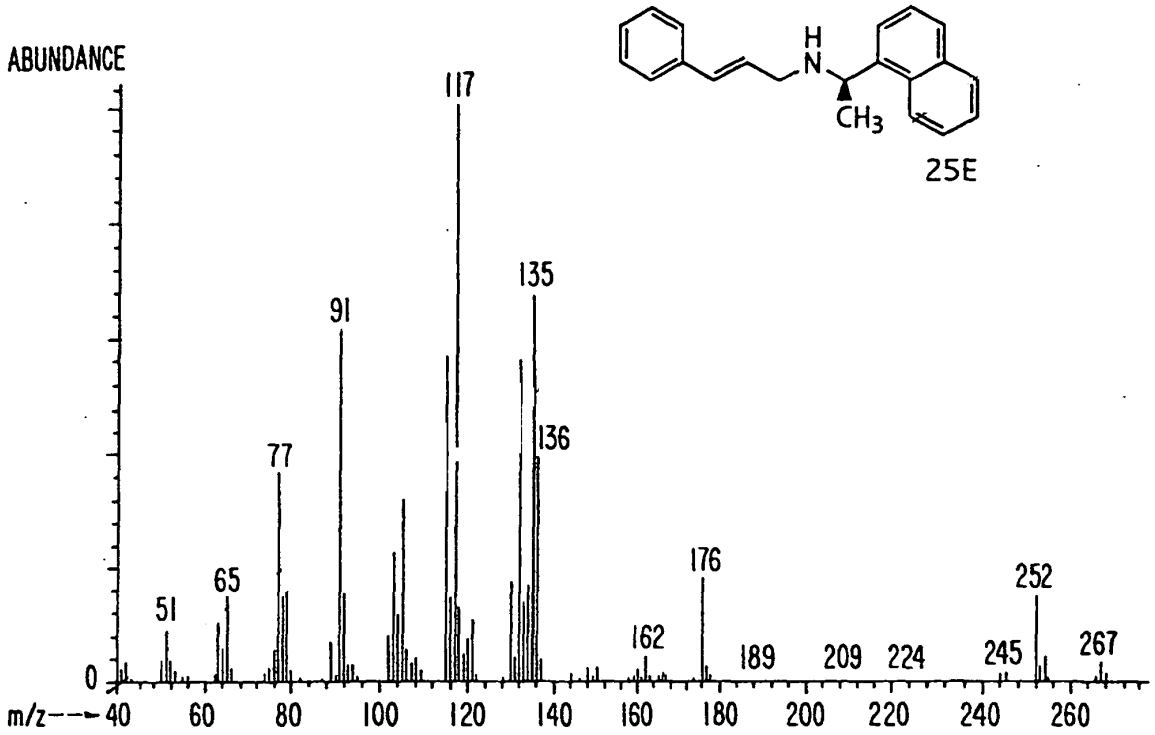
60
80
100
120
140
160
180
200
220
240
260
280
CH3
H
N
OCH3
CH3
12F

FIG. 35.


ABUNDANCE
117
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162
189
209
224
245
267
0
m/z
40
60
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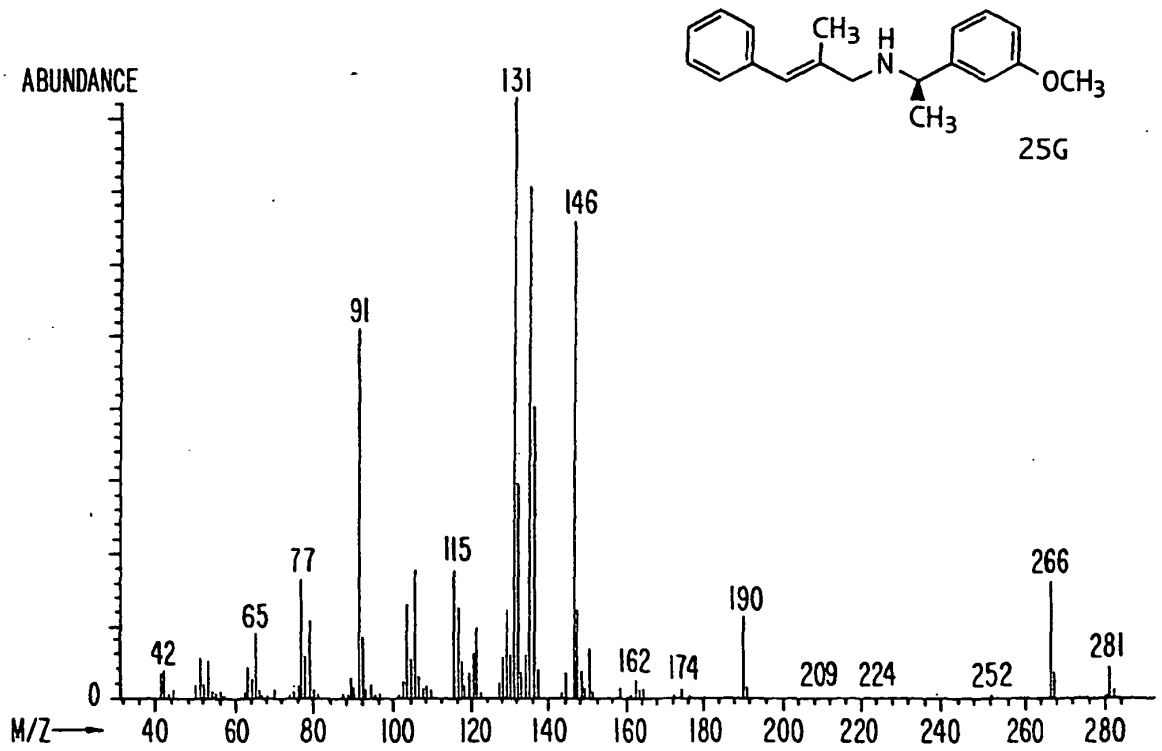
100
120
140
160
180
200
220
240
260
H
N
CH3
25E

FIG. 91.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77
115
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42
190
266
281
162
174
209
224
252
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
CH3
H
N
OCH3
CH3
25G

FIG. 92.

REFERENCES CITED IN THE DESCRIPTION

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