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

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References Cited U.S. PATENT DOCUMENTS

2,276,618	3/1942	Kulz et al	260/520.8
2,930,731	3/1960	Heinzelmann et al.	167/52
2,949,359	8/1960	Blout et al	96/66
3,202,711	8/1965	Fruhstorfer et al	
3,262,977	7/1966	Harsanyi et al	260/570
3,493,662	2/1970	Duerr et al	424/330
3,536,712	10/1970	Keck et al	260/253
3,689,524	9/1972	Jack et al	260/471 A
3,842,067	10/1974	Sarantakis	260/112.5
3,862,925	1/1975	Sarantakis	260/112.5
3,972,859	8/1976	Fujino et al	260/112.5
4,000,197	12/1976	Barfknecht et al	260/570.8 R
4,014,937	3/1977	Richardson	260/570.8 R
4,098,890	7/1978	Molloy	424/248.4
4,105,602	8/1978	Colescott et al	260/8
4,242,355	12/1980	Nedelec et al	424/275
4,289,787	9/1981	Molloy et al	424/329
4,360,511	11/1982	Baldwin et al	
4,391,826	7/1983	Mills et al	424/324
4,487,965	12/1984	Himmele et al	564/454
4,587,253	5/1986	Halczenko et al	514/289
4,591,605	5/1986	Ray	
4,608,391	8/1986	Ginos et al	

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

621300	12/1962	(BE).
1065857	11/1992	(CH).
217009	1/1984	(CS).
1231690	1/1967	(DE).

2541184	4/1976	(DE).
2825961	3/1980	(DE).
0009702	9/1979	(EP).
0005848	12/1979	(EP).
0007204	1/1980	(EP).
0015505	9/1980	(EP).
0023385	2/1981	(EP).
0 44 158 A1	1/1982	(EP).
0101069	8/1983	(EP).
0092787	11/1983	(EP).
0200101	12/1986	(EP).
0253327	1/1988	(EP).
0270376	7/1988	(EP).
0289287	11/1988	(EP).
0309100	3/1989	(EP).
0395357	10/1990	(EP).
0408284	1/1991	(EP).
0455510	3/1991	(EP).
0224163	10/1991	(EP).
0508307	10/1992	(EP).

(List continued on next page.)

OTHER PUBLICATIONS

Fox et al; Journal of Bone and Mineral Research; 8:S181, abstract 260; Suppl. 1, Aug. 1993.

Majewski et al; Canadian J.Chem; 73; 1616-1626, 1995.

Hashimoto et al;Synlett;961-962, Sep. 1995.

Majewski et al;Tetrahedron:Asymmetry;vol. 6;No. 8;pp 1837–1840, 1995.

Polniaszek et al; J.Am. Chem. Soc; 111; 4859-4863, 1989.

Kametani et al; J.Chem.Soc:Perkin Trans1;579-581, 1977. Polniaszek et al; Tetrahedron Letters; vol. 31; No. 6; pp797–800, 1990.

Merck Index;; Eleventh Ed; #2993; p.2997, 1989.

Walker, et al., J. Med. Chem., 9(4), 624-30 (1966), "Synthesis of Varied Heterocyclic and Substituted Aryl Alkyl Secondary Amines, Related Schiff Bases, and Amides".

Burke, et al., J. Org. Chem. 28, 1098-1100 (1963), "Mono-1,3-benzoxazines from Hydroquinone".

West, et al., J. Am. Pharm. Assoc. 46, 58-61 (1957), "A pharmacological Study of a Series of Aralkylamines".

Anderson and Santi, "Phenylalanyl Transfer Ribonucleic Acid Synthase from Escherichia coli B. Potent Inhibition by Analogues of N-Benzyl-2-phenylethylamine," J. Med. Chem. 19:1270-1275 (1976).

Arjona et al., "Sterochemistry of the reduction of the imino group. IV. Sterochemistry of the reduction of N-(1-phenylethyl)-1-alkyl-1-arylmethanimines," Quim. Ser. C 81(1):23-29 (1985).

(List continued on next page.)

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ABSTRACT (57)

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. Preferably, the compound can mimic or block the effect of extracellular Ca2+ on a calcium receptor.

46 Claims, 104 Drawing Sheets



U.S. PATENT DOCUMENTS

4,609,494	9/1986	Baldwin et al 544/250
4,647,446	3/1987	Sargent et al 424/1.1
4,661,635	4/1987	Carson 564/374
4,675,321	6/1987	Baldwin et al 514/274
4,677,101	6/1987	Claremon et al 514/215
4,769,483	9/1988	Lombardi et al 560/19
4,797,411	1/1989	Crugnola et al 514/357
4,808,718	2/1989	Hartman et al 546/14
4,839,369	6/1989	Youssefyeh et al 514/314
4,916,145	4/1990	Tilley et al 514/357
4,925,664	5/1990	Jackson et al 424/537
4,925,873	5/1990	Friedhoff et al 514/469
4,967,003	10/1990	Rentzea et al 564/381
4,988,730	1/1991	Korbonits et al 514/466
5,001,251	3/1991	MacManus et al 558/255
5,011,834	4/1991	Weber et al 514/212
5,021,599	6/1991	Beer et al 556/142
5,030,576	7/1991	Dull et al 435/69.7
5,034,514	7/1991	Nitecki et al 530/390
5,053,337	10/1991	Weinshank et al 435/240.2
5,064,657	11/1991	Jackson et al 424/537
5,073,648	12/1991	Hagishita et al 564/374
5,075,338	12/1991	Knoll et al 514/634
5,082,837	1/1992	Palfreyman 514/183
5,334,628	8/1994	Maeda et al 514/311
5,403,861	4/1995	Goldin et al 514/634
5,688,938	11/1997	Brown et al 536/23.5
5,763,569	6/1998	Brown et al 530/324

FOREIGN PATENT DOCUMENTS

	0443606	5/1995	(EP).
	1109924	4/1968	(GB).
	1448437	7/1974	(GB).
	1464209	9/1977	(GB).
	2113089	11/1982	(GB).
	2213818	8/1989	(GB).
	1079091	9/1997	(GB).
:	53-90272	8/1978	(JP).
	59-50358	3/1984	(JP) .
	2200658	8/1990	(JP) .
	8204052	11/1982	(WO).
	8906135	7/1989	(WO).
	8909834	10/1989	(WO).
	9100853	1/1991	(WO).
	9109594	7/1991	(WO).
	9207829	5/1992	(WO).
	9214709	9/1992	(WO).
	9304373	4/1993	(WO).
	9310073	5/1993	(WO).
	9315044	5/1993	(WO).
	9313052	8/1993	(WO).
	9418959	9/1994	(WO).
	9511221	4/1995	(WO).
	9518134	7/1995	(WO).
/O	9518134	7/1995	(WO).
	9521815	8/1995	(WO).

OTHER PUBLICATIONS

Barney et al., "A Convenient Synthesis of Hindered Amines and α-Trifluoromethylamines from Ketones," *Tetrahedron Letters* 31:5547–5550 (1990).

Batra and Alenfall, "Effects of Diverse Categories of Drugs on Human Colon Tumour Cell Proliferation," *Anticancer Research* 11:1221–1224 (1991).

Becalski et al., "Catalytic asymmetric hydrogenation of imines. Use of rhodium(I)/phosphine complexes and characterization of rhodium(I)/imine complexes," *Chemical Abstracts* 116:558 at Abstract No. 14742U (1992).

Bertz et al., "Asymmetric Induction with Amidocuprates," *J. Org. Chem.* 51:4953–4949 (1986).

Boyd et al., "Dynamic Sterochemistry of Imines and Derivatives. Part 18. Photosynthesis and Photoracemization of Optically Active Oxaziridines," *J. Chem. Soc. Perkin Trans. I* 4:849–855 (1985).

Bringmann et al., "The Enantioselective Synthesis of Optically Active, Benzene Nucleus–Substituted 1–Phenylethylamines from the Corresponding Acetophenones," *Leibigs Ann. Chem.* 5:795–805 (1990).

Bringmann et al., "Enantiomerically Pure N–Boc Protected β –Keto–65 –Amino Acid Esters from Simple Keto Precursors: A Novel, Stereocontrolled Approach to Statine Derivatives with Any Desired Configuration," *Synlet Letters* pp. 253–255 (1990).

Brown et al., "A Comparison of the Effects of Divalent and Trivalent Cations on Parathyroid Hormone Release, 3',5'—Cyclic—Adenosine Monophosphate Accumulation, and the Levels of Inositol Phosphates in Bovine Parathyroid Cells," *Endocrinology* 127:1064–1071 (1990).

Brown et al., "Cloning and characterization of an extracellular Ca²⁺ sensing receptor from bovine parathryoid," *Nature* 366:575–580 (1993).

Brown, "Extracellular Ca²⁺ Sensing, Regulation of Parathyroid Cell Function and Role of Ca²⁺ and Other Ions as Extracellular (First) Messengers," *Physiological Reviews* 71:371–411 (1991).

Brown et al., "High Extracellular Ca²⁺ and Mg²⁺ Stimulate Accumulation of Inositol Phosphates in Bovine Parathyroid Cells," *FEBS Letters* 218:113–118 (1987).

Brown et al., "Neomycin Mimics the Effects of High Extracellular Calcium Concentrations on Parathyroid Function in Dispersed Bovine Parathyroid Cells," *Endocrinology* 128:3047–3054 (1991).

Brown et al., "Polyarginine, Polylysine, and Protamine Mimic the Effects of High Extracellular Calcium Concentrations on Dispersed Bovine Parathyroid Cells," *Journal of Bone and Mineral Research* 6:1217–1225 (1991).

Capuano et al., "Characterization of the Human Calcium Receptor Gene," *Journal of Bone and Mineral Research* 9(1):S145 at abstract No. 98 (1994).

Chemical Abstracts Formula Index, vol. 110 p. 537F (1989). Chemical Abstracts Formula Index, vol. 110 p. 1793F (1989).

Chen et al., "Injection of Bovine Parathyroid Poly(A)* RNA into Xenopus Oocytes Confers Sensitivity to High Extracellular Calcium," *Journal of Bone and Mineral Research* 9:293–300 (1994).

Chen and Brown, "The Diltiazem Analog TA–3090 Mimics the Actions of High Extracellular Ca²⁺ on Parathyroid Function in Dispersed Bovine Parathyroid Cells," *Journal of Bone and Mineral Research* 5:581–587 (1990).

Clifton et al., "Arylethanolamines derived from salicylamide with alpha—and beta—adrenoceptor blocking activities. Preparation of labetalol, its enantiomers and related salicylamides," *J. Med. Chem.* 25:670–679 (1982).

Danks, "Reaction of Hydride Transfer Reducing Agents with (1–Heterodiene) Tricarbonyliron(0) Complexes and the Synthesis of Saturated Amines and Alcohols," *Tetrahedron Letters* 35:4177–4178 (1994).

Davies and Ichihara, "Asymmetric Synthesis of R- β -Amino Butanoic Acid and S- β -Tyrosine: Homochiral Lithium Amide Equivalents for Michael Additions to α,β -Unsaturated Esters," *Tetrahedron Asymmetry* 2:183–186 (1991).



W

De Feo et al., "Natriuretic Peptide Receptors Regulate Endothelin Synthesis and Release From Parathyroid Cells," *Proc. Natl. Acad. Sci. USA* 88:6496–6500 (1991).

Fox et al., "A First Generation Calcimimetic Compound (NPS R-568) That Acts on the Parathyroid Cell Calcium Receptor: A Novel Therapeutic Approach for Hyperparathyroidism," *Journal of Bone and Mineral Research* 8(1):S181 at abstract No. 260 (1993).

Fox et al., "NPS R-568 Acts on Calcium Receptors to Inhibit Parathyroid Hormone and Stimulate Calcitonin Secretion: ANovel Therapeutic Approach for Hyperparathyroidisum," *J. American Society of Nephrology* 4:719 at abstract No. 120P (1993).

Fox et al., "NPS R-568 Inhibits Parathyroid Hormone Secretion and Stimulates Calcitonin Secretion in Hyperparathyroid Rats with Chronic Renal Failure," *J. American Society of Nephrology* 4:719 at abstract No. 69P (1993).

Fox et al., "Parathyroid Gland Calcium Receptor Gene Expression is Unaffected by Chronic Renal Failure or Low Dietary Calcium in Rats," *J. Am. Soc. Nephrology* 5:879 at abstract No. 90P (1994).

Fox et al., "Physiology Relevant PTH Levels are Anabolic on Bone in Ovariectomized Rats," *Bone* 16(Supplement):194S at abstract No. 434 (1995).

Fox et al., "Prevention of Hypocalcemia Prolongs the Plasma Parathyroid Hormone and Calcitonin Responses to the Calcimimetic Compound NPS R-568 in Rats," *Journal of Bone and Mineral Research* 9(1):S409 at abstract No. C396 (1994).

Fraser et al., "Substitution α to the Nitrogen in Dibenzylamine via Carbanion Intermediates," *Can. J. Chem.* 51:1109–1115 (1973).

Freifelder, "Selective Hydrogenolysis. Dehalogenation in the Presence of N-Benzyl Linkage," *J. Org. Chem.* 31(11):3875–3877 (1966).

Fuji et al., "Endothelin as an Autocrine Factor in the Regulation of Parathyroid Cells," *Proc. Natl. Acad. Sci. USA* 88:4235–4239 (1991).

Fuleihan et al., "Effects of the Lectin Concanavalin—A on the Regulation of Second Messengers and Parathyroid Hormone Release by Extracellular Ca²⁺ in Bovine Parathyroid Cells," *Endocrinology* 128:2931–2936 (1991).

Fuleihan and Brown, "Effect on the Lectin Concanavalin—A on Calcium—Regulated Adenosine 3', 5'—Monophosphate Accumulation in Bovine Parathyroid Cells," *Endocrinology* 126:1996–2002 (1990).

Garrett et al., "Cloning and Expression of a G-Protein-Coupled Calcium Receptor From a Human Parathyroid Adenoma," *Journal of Bone and Mineral Research* 8(Supplement 1):S148 at abstract No. 125 (1993).

Garrett et al., "Expression of the Parathyroid Calcium Receptor Gene in C-Cells," *Journal of Bone and Mineral Research* 9(1):S409 at abstract No. C398 (1994).

Gracheva et al., "Stereodirection of Ketimine Reduction Reactions," *Zhural Organicheskoi Khimii* 9(6):1235–1239 (1973).

Gracheva et al., "The Stereoselectivity of the Reactions of Schiff Bases with Organomagnesium Compounds," *Zhural Organicheskoi Khimii* 10(3):577–561 (1974).

Grethe et al., "Syntheses in the Isoquinoline Series. Synthesis of 2,3–Dihydro–4(1H)–isoquinolones," *J. Org. Chem.* 33(2):491–494 (1968).

Hammerland et al., "Mechanism of Action of the Calcimimetic Compounds NPS R-467 and NPS R-568 in Xenopus Oocytes Expressing a Bovine Parathyroid Cell Calcium Receptor," *Journal of Bone and Mineral Research* 8(Supplement 1):S133 at abstract No. 65 (1993).

Harootunian et al., "Effect of Calcitonin and Extracellular Calcium on Cytosolic Levels of Cyclic AMP and Ca²⁺ in Rabbit Osteoclasts," *Journal of Bone and Mineral Research* 9(1):S246 at abstract No. B66 (1994).

Hashimoto et al., "Highly Diastereoselective Addition of Organometallic Reagents to Chiral Imines Derived from 1–(2–Methoxyphenyl)ethylamine," *Synlett Letters* pp. 961–962 (1995).

Hawkins et al., "The Effects of High Extracellular Ca²⁺ and Mg²⁺ Concentrations on the Levels of Inositol 1,3,4,5–Tetrakisphosphate in Bovine Parathyroid Cells," *Endocrinology* 124:838–844 (1989).

Heath et al., "Inhibition of Human Parathyroid Hormone Secretion In Vivo by NPS R-568, a Calcimimetic Drug that Targets the Parathyroid Cell-Surface Calcium Receptor," *Bone* 16(Supplement):85S at abstract No. 23 (1995).

Hiroi et al., "A Highly Efficient and Recyclable Chiral Director for Asymmetric Synthesis of Sulfoxides," *Chemistry Letters* pp. 1595–1598 (1980).

Hiroi et al., "Studies on Chiral Organo–Sulfur Compounds. I. Asymmetric Synthesis of Sulfoxides with Optically Active o–Aminoalkylphenol Derivatives," *Chem. Pharm. Bull.* 31:3471–3485 (1983).

Höltje and Maurhofer, "Conformational Analysis on Calcium Channel Active Diphenylalkylamines, Diphenylbutylpiperidines, Phenylalkylamines, and Perhexiline," *Quant. Struct.—Act. Relat.* 8:259–265 (1989).

Hu et al., "Lithium hydride elimination in the reactions of organolithium compounds with imines: synthesis of secondary amines with branched groups," *C.R. Acad. Sci. Paris Ser. C* 284(4):195–198 (1977).

Hung et al., "Coupling of the Porcine Calcitonin Receptor to Cytosolic Ca²⁺ and cAMP Levels in Xenopus Oocytes," *Journal of Bone and Mineral Research* 9(1):S410 at abstract No. C400 (1994).

Hutton et al., "Organic Reagents for the Precipitation of Nitrate Ion. Part I. N-Substituted 1-napthylmethylamines," *J. Chem. Soc.* (A) 11:1573–1579 (1966).

Ikegami and Yamada, "Chemistry of Sodium Borohydride and Diborane. II. Reduction of Schiff Bases with Diborane in Tetrahydrofuran," *Chem. Pharm. Bull.* 14(12):1389–1399 (1966).

Jasys et al., "The Total Synthesis of Argiotoxins 636, 659 and 673," *Tetrahedron Letters* 29:6223–6226 (1988).

Joshi and Mehrotra, "Reductive Coupling In Substituted Imines with Aluminium-Amalgam in Moist Ether," *Nat. Acad. Sci. Letters* (*India*) 3:268–272 (1980).

Juaristi et al., "Use of N,N'-Dimethylpropyleneurea (DMPU) as Solvent in the Efficient Preparation of Enantiomerically Pure Secondary Amines," *Synthesis* pp. 1243–1246 (1993).

Kametani et al., "Studies on the Synthesis of Heterocyclic Compounds. Part 687. Asymmetric Synthesis of Salsolidine," *J. Chem. Soc. Perkin Trans.* 1 pp. 579–581 (1977).

Kang et al., "Rhodium(I)—catalysed Asymmetric Hydrogenation of Imines," *J. Chem. Soc. Chem. Commun.* pp. 1466–1467 (1988).



Katritzky et al., "Convenient Preparations of Imines and Symmetrical Secondary Amines Possessing Primary or Secondary Alkyl Groups," *Synthesis* 9:703–708 (1991).

Katz et al., "Structure–Function Relationships for the Effects of Various Aminoglycoside Antibotics on Dispersed Bovine Parathyroid Cells," *Endocrinology* 131:903–910 (1992).

Kienzle et al., "1,5—Dihydroimidazoquinazolinones as blood platelet aggregation inhibitors," *Eur. J. Med. Chem.—Chem. Ther.* 17:547–556 (1982).

Kifor and Brown, "Relationship between Diacylglycerol Levels and Extracellular Ca²⁺ in Dispersed Bovine Parathyroid Cells," *Endocrinology* 123:2723–2729 (1988).

Koenig et al., "Polyamines Mediate Androgenic Stimulation of Clacum Fluxes and Membrane Transport in Rat Heart Myocytes," *Circulation Research* 64:415–426 (1989).

Komeyoshi and Kudo, "Optically active amines and their manufacture, intermediates and uses," *Chemical Abstracts* 121:1060 at Abstract No. 230462Y (1994).

Kozlov et al., "Reductive animation of 1–acetylcyclohexene by nitriles," *Vestsi Akad. Navuk BSSR, Ser. Khim. Navuk* pp. 55–58 (1977).

Langlois et al., "Asymmetric synthesis of amines by hydrosilylation of imines catalyzed by a chiral complex of rhodium," *Tetrahedron Lett.* 49:4865–4868 (1973).

Lensink and De Vries, "Diastereoselective hydrogenation and kinetic resolution of imines using rhodium/diphosphine catalyzed hydrogenation," *Tetrahedron: Asymmetry* 4:215–222 (1993).

Lensink and de Vries, "Improving Enantioselectivity by Using a Mono–Sulphonated Diphosphine as Ligand for Homogenous Imine Hydrogenation," *Tetrahedron:Assymetry* 3(2):235–238 (1992).

Leszkovzky et al., "The Pharmacology of Diphenylalkyl Derivatives," *Acta Physiologica Academiae Scientiarum Hungaricae Tomus* 29:283–297 (1966).

Levine, *Pharmacology: Drug Actions and Reactions*, Little Brown and Company, Inc. pp. 192–196 (1990).

Lopez–Barneo and Armstrong, "Depolarizing Response of Rat Parathyroid Cells to Divalent Cations," *J. Gen. Physiol.* 82:269–294 (1983).

Majewski and MacKinnon, "Enantioselective deprotonation of protected 4–hydroxycyclohexanones," *Can. J. Chem.* 72:1699–1704 (1994).

Mattson et al., "An Improved Method for Reductive Alkylation of Amines Using Titanium(IV) Isopropoxide and Sodium Cyanoborohydride," *J. Org. Chem.* 55:2552–2554 (1990).

Merck Index, 11th Edition, Monograph No. 8699, pp. 420, 1379 (1989).

Merck Index, 11th Edition, Monograph No. 3916, p. 623 (1989)

Merrifield, "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide," *J. Amer. Chem. Society* 85:2149–2154 (1963).

Mithal et al., "Highly Purified Sheep C-Cells Express an Extracellular Ca²⁺ Receptor Similar to that Present in Parathyroid," *Journal of Bone and Mineral Research* 9(1):S282 at abstract No. B209 (1994).

Mori et al., "Formic Acid Reduction. XI. Reduction of Schiff Bases," *Chem. Pharm. Bull.* 19:1722–1727 (1971).

Muff et al., "Regulation of Hormone Secretion and Cytosolic Ca²⁺ by Extracellular Ca²⁺ in Parathyroid Cells and C–Cell: Role of Voltage–Senstive Ca²⁺ Channels," *Archives of Biochemistry and Biophysics* 265:128–135 (1988).

Nason et al., "Synthesis of Neurotoxic Nephlla Spider Venoms: NSTX-3 and JSTX-3," *Tetrahedron Letters* 30:2337–2340 (1989).

Nemeth, "Ca²⁺ Receptor–Dependent Regulation of Cellular Functions," *NIPS* 10:1–5 (1995) Check 1–15.

Nemeth and Scarpa, "Cystolic Ca²⁺ and the regulation of secretion in parathyroid cells," *FEBS Letters* 203(1):15–19 (1986).

Nemeth, "Evidence for the Presence of a Novel Ca²⁺-Binding Protein (Ca²⁺ Receptor) on the Surface of Parathyroid Cells," *Calcium-Binding Proteins in Health and Disease*, Norman et al. editors, Academic Press, Inc., San Diego, pp. 36–38 (1987).

Nemeth and Scarpa, "Rapid Mobilization of Cellular Ca²⁺ in Bocine Parathyroid Cells Evoked by Extracellular Divalent Cations—Evidence for a Cell Surface Calcium Receptor," *J. Biol. Chem.* 262(11):5188–5196 (1987).

Nemeth and Scarpa, "Receptor-Dependent Mobilization of Cellular Ca²⁺ and the Regulation of Hormone Secretion in Parathyroid Cells," *Calcium Regulation and Bone Metabolism: Basic and Clinical Aspects* 9:167–171 (1987).

Nemeth, "Regulation of cystolic calcium by extracellular divalent cations in C-cells and parathyroid cells," *Cell Calcium* 11:323–327 (1990).

Nemeth et al., "Screening of compounds with potential action against calcium receptors and their use in therapy of disorders of calcium metabolism," *Chemical Abstracts* 122(1):P1057y (1995).

Nemeth and Scarpa, "Spermine Evokes the Rapid Mobilization of Cellular Ca²⁺ in Parathyroid Cells," *Calcium–Binding Proteins in Health and Disease*, Normal et al. editors, Academic Press, Inc., San Diego, pp. 33–35 (1987). Nemeth and Carafoli, "The role of extracellular calcium in the regulation of intracellular calcium and cell function," *Cell Calcium* 11:319–321 (1990).

Neuvonen and Pihlaja, "Studies on the Benzoxazine Series. Part 3—Preparation and ¹³C NMR Structural Study of γ Effects of Some N–Substituted 3,4–Dihydro–2H–1,3–benzoxazines," *Magnetic Resonance in Chemistry* 28:239–245 (1990).

Opie, "Calcium Channel Antagonists Part V: Second–Generation Agents," *Cardiovascular Drugs and Therapy* 2:191–203 (1988).

Paulsen–Sorman et al., "Cytochrome P–455 nm Complex Formation in the Metabolism of Phenylalkylamines. 8. Stereoselectivity in Metabolic Intermediary Complex Formation with a Series of Chiral 2–Substituted 1–Phenyl–2–aminoethanes," *J. Med. Chem.* 27:342–346 (1984).

Polniaszek and Dillard, "Diastereoselective Addition of Organometallic Reagents to Chiral Immune Ions: Synthesis of (S)–(+)–Cryptostyline I," *Tetrahedron Letters* 31:797–800 (1990).

Racke et al., "Functional expression of the parathyroid cell calcium receptor in Xenopus oocytes," *FEBS Letters* 333(1, 2):132–136 (1993).

Racke et al., "Functional Expression of the Parathyroid Cell Calcium Receptor in Xenopus Oocytes," *Journal of Bone and Mineral Research* Supplement 1, 6:S118 at abstract No. 141 (1991).

Rai and Singh, "Synthesis and reduction of ketimines," *Indian J. Chem. Sect. B* 14B:377–378 (1976).



Rogers et al., "Calcium Receptor Expression in the Parathyroid Glands of Vitamin D–Deficient Rats is not Regulated by Plasma Caclium and 1,25(OH)₂D₃," *Journal of Bone and Mineral Research* 9(1):S409 at abstract No. C392 (1994). Rogers et al., "Localization of Calcium Receptor mRNA in Rat Thyroid and Parathyroid Glands Using In Situ Hybridization Histochemistry," *Journal of Bone and Mineral Research* 9(1):S409 at abstract No. C390 (1994).

Rogers et al., "The Calcimimetic Compound NPS467 Reduces Plasma Calcium in a Dose–Dependent and Stero–Specific Manner," *Journal of Bone and Mineral Research* 8(Supplement 1):S180 at abstract No. 254 (1993). Schäfer et al., "Polyamine Toxins from Spiders and Wasps," *The Alkaloids* 45:1–125 (1994).

Schwartz and Hu, "Synthesis of Hindered Secondary Amines via Grignard Reagent Addition to Ketonitrones," *Tetrahedron Letters* 13:1689–1692 (1992).

Seely et al., "The Calcium Channel Blocker Diltiazem Lowers Serum Parathyroid Hormone Levels in Vivo and in Vitro," *Journal of Clinical Endocrinology and Metabolism* 68(6):1007–1012 (1989).

Shoback and Chen, "Injection of Poly (A)* RNA from Bovine Parathyroid Tissue into Xenopus Oocytes Confers Sensitivity to Extracellular Calcium," *Journal of Bone and Mineral Research* 6(Supplement 1):S135 at abstract No. 207 (1991).

Standridge et al., "Phenylalkylamines with Potential Psychotherapeutic Utility. 2. Nuclear Substituted 2–Amino–1–phenylbutanes," *J. Med. Chem.* 23:154–162 (1980).

Standridge et al., "Phenylalkylamines with Potential Psychotherapeutic Utility. 1. 2–Amino–1–(2, 5–dimethoxy–4–methylphenyl) butane," *J. Med. Chem.* 19:1400–1404 (1976).

Steffey and Nemeth, "Extracellular Calcium—Sensing Mechanisms on Osteoclasts and Parathyroid Cells are Pharmacologically Distinct," *Journal of Bone and Mineral Research* 8(Supplement 11):S384 at at abstract No. 1071 (1993).

Steffey et al., "Calcimimetics: Structurally and Mechanistically Novel Compounds that Inhibit Hormone Secretion From Parathyroid Cells," *Journal of Bone and Mineral Research* 8(Supplement 1):S175 at abstract No. 236 (1993).

Triggle et al., "Ca²⁺ Channel Ligands: Structure–Function Relationships of the 1,4–Dihydropyridines," *Medicinal Research Reviews* 9(2):123–180 (1989).

Van Dijk and Moed, "Synthesis of β -Phenylethyloamine Derivatives X¹* N-(Hydroxy- and Methoxy-Aralkyl) Derivatives," *Recl. Trav. Chim. Pays-Bas* 92:1281–1297 (1973).

Van Niel and Pandit, "NADH Models XXI. Steroselective Reduction of Chiral Imines with Hantzsch Ester," *Tetrahedron* 41:6065–6011 (1985).

Wang and Bäckvall, "Ruthenium-catalysed Transfer Hydrogenation of Imines by Propan-2-ol," *J. Chem. Soc. Commun.* pp. 980–982 (1992).

Witkop "Nonenzymatic Methods for the Preferential and Selective Cleavage and Modification of Proteins," *Advances in Protein Chemistry*, Anfinsen et al. editors, Academic Press, Inc., New York, 16:221–321 (1961).

Yamaguchi et al., "Asymmetric Reduction with Chiral Reagents from Lithium Aluminum Hydride and (S)–(–)–N–(ο–Substituted benzyl)–α–phenylethylamines," *J. Org. Chem.* 42:1578–1581 (1977).

Zaidi, "Calcium Receptors' on Eukaryotic Cells with Special Reference to the Osteoclast," *Bioscience Reports* 10:493–507 (1990).

Zaidi et al., "Intracellular calcium in the control of osteoclast function. II. Paradoxical elevation of cytosolic free calcium by verapamil," *Biochemical and Biophysical Research Communications* 167:807–812 (1990).

Anderson and Santi, "Phenylalanyl Transfer Ribonucleic Acid Synthetase from *Escherichia coli* B. Potent Inhibition by Analogues of N–Benzyl–2–phenylethylamine," *J. Med. Chem.* 19:1270–1275 (1976).

Langlois et al., "Asymmetric synthesis of amines by hydrosilyation of imines catalyzed by a chiral complex of rhodium," *Tetrahedron Lett.* 49:4865–4868 (1973).

Larsson et al., "Paradoxical effects of K⁺ and D-600 on parathyroid hormone secretion and cytoplasmic Ca²⁺ in normal bovine and pathological human parathyroid cells," *Biochimica et Biophysica Acta* 847:263–269 (1985).



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