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

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(56) **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.	260/570
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.	424/1.5
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	514/579
4,608,391	8/1986	Ginos et al.	514/654

(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," *An. Quim. Ser. C* 81(1):23–29 (1985).

(List continued on next page.)

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(57) **ABSTRACT**

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 Ca^{2+} 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) .
WO 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 Ca^{2+} sensing receptor from bovine parathryoid," *Nature* 366:575–580 (1993).

Brown, "Extracellular Ca^{2+} Sensing, Regulation of Parathyroid Cell Function and Role of Ca^{2+} and Other Ions as Extracellular (First) Messengers," *Physiological Reviews* 71:371–411 (1991).

Brown et al., "High Extracellular Ca^{2+} and Mg^{2+} 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 Ca^{2+} 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).

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: A Novel 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 Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} and Mg^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} by Extracellular Ca^{2+} in Parathyroid Cells and C–Cell: Role of Voltage–Senstive Ca^{2+} 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, "Ca^{2+} Receptor–Dependent Regulation of Cellular Functions," *NIPS* 10:1–5 (1995) Check 1–15.
Nemeth and Scarpa, "Cystolic Ca^{2+} and the regulation of secretion in parathyroid cells," *FEBS Letters* 203(1):15–19 (1986).
Nemeth, "Evidence for the Presence of a Novel Ca^{2+}–Binding Protein (Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 ^{13}C 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 $1,25(OH)_2D_3$," *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., "Ca^{2+} 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 X^{1*} 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–(o–Substituted benzyl)–α–phenylethylamines," *J. Org. Chem.* 42:1578–1581 (1977).

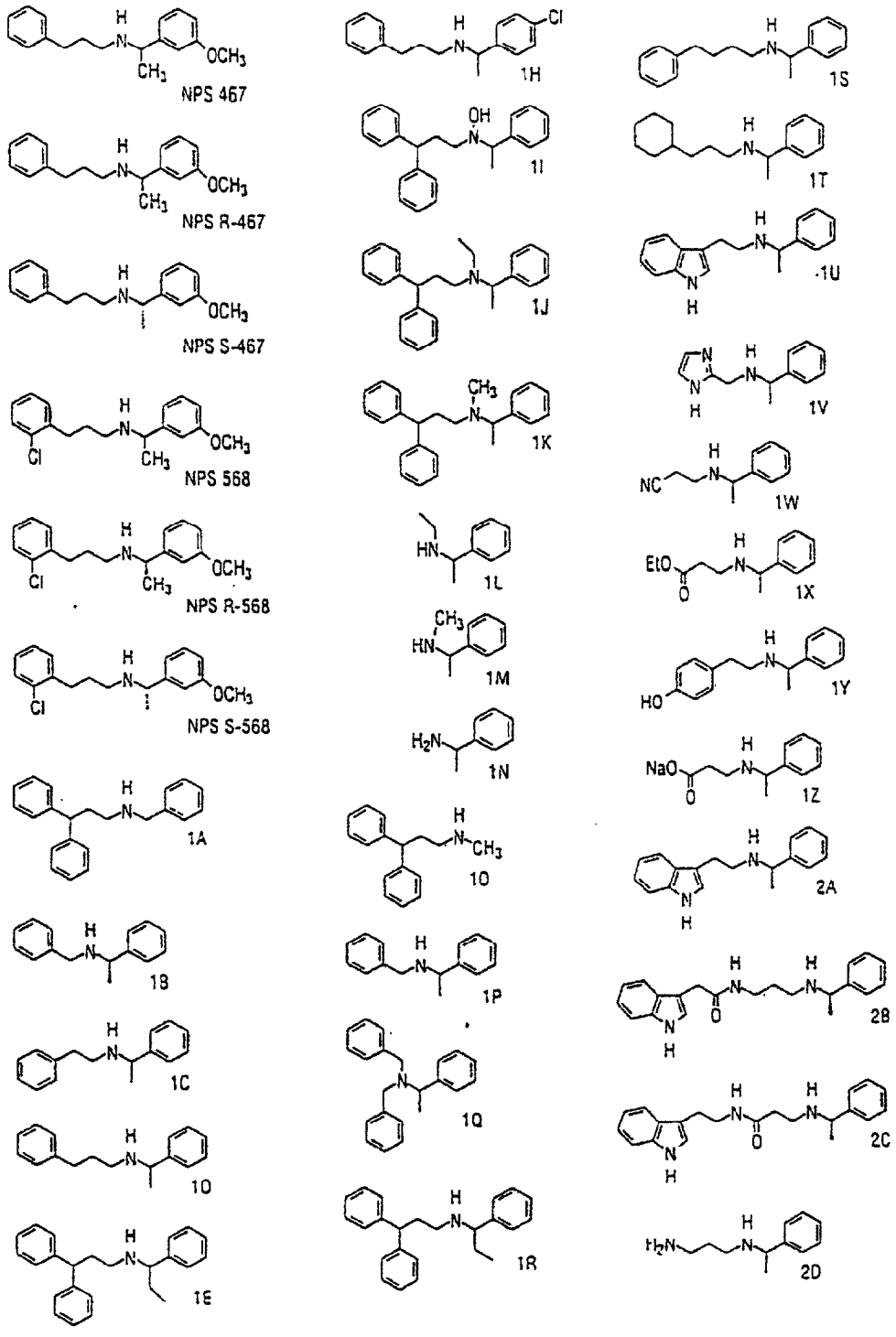
Zaidi, "'Calcium Receptors' on Eukaryotic Cells with Special Reference to the Osteoclast," *Bioscience Reports* 10:493–507 (1990).

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 Ca^{2+} in normal bovine and pathological human parathyroid cells," *Biochimica et Biophysica Acta* 847:263–269 (1985).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NPS S-467
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NPS R-568
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1K
1L
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1O
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1Q
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1W
1X
1Y
1Z
2A
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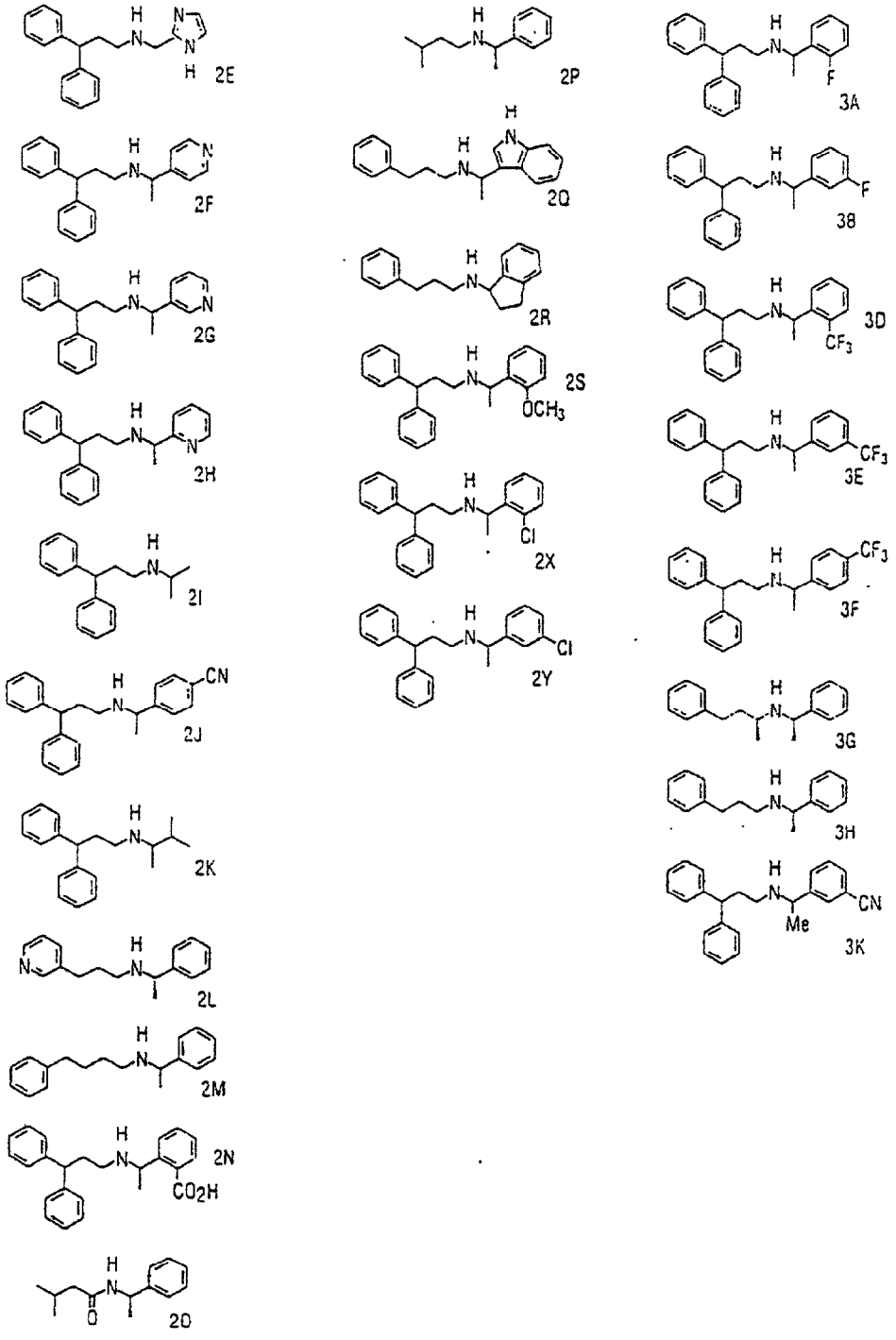
2C
2D

FIG. 1a.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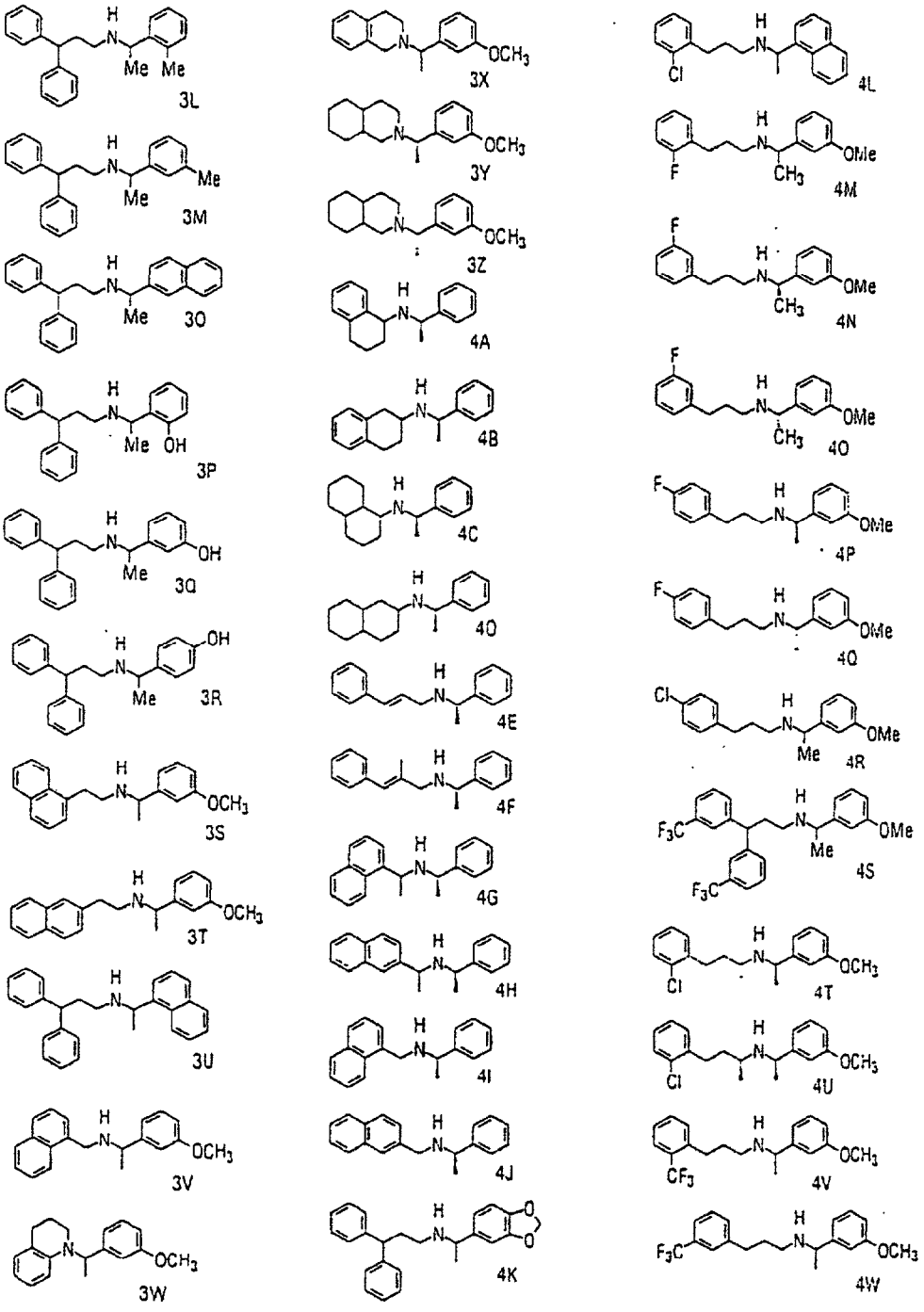
2X
2Y
3A
3B
3D
3E
3F
3G
3H
3K

FIG. 1b.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3X
3Y
3Z
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4B
4C
4D
4E
4F
4G
4H
4I
4J
4K
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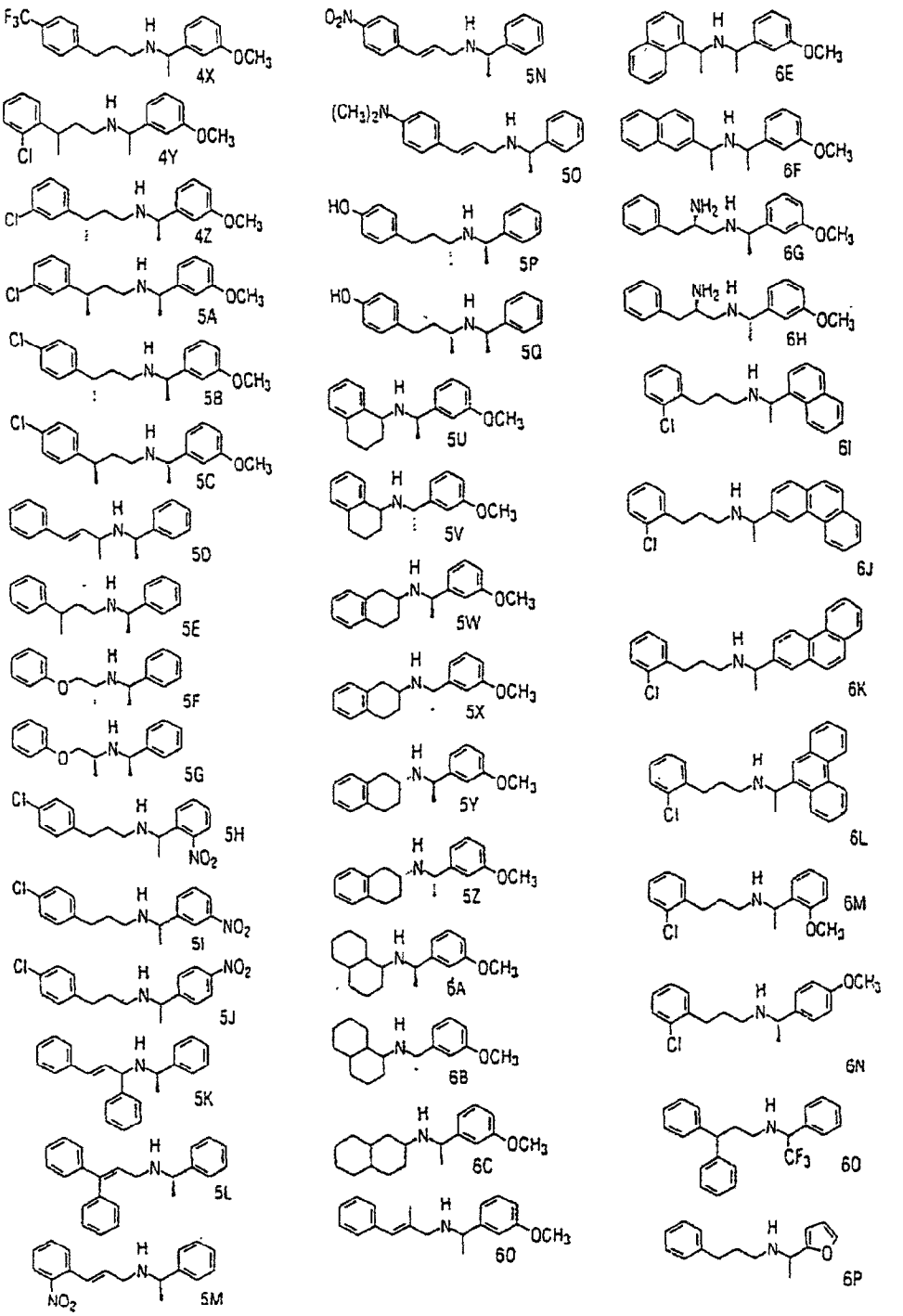
4W

FIG. 1c.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5N
5O
5P
5Q
5U
5V
5W
5X
5Y
5Z
6A
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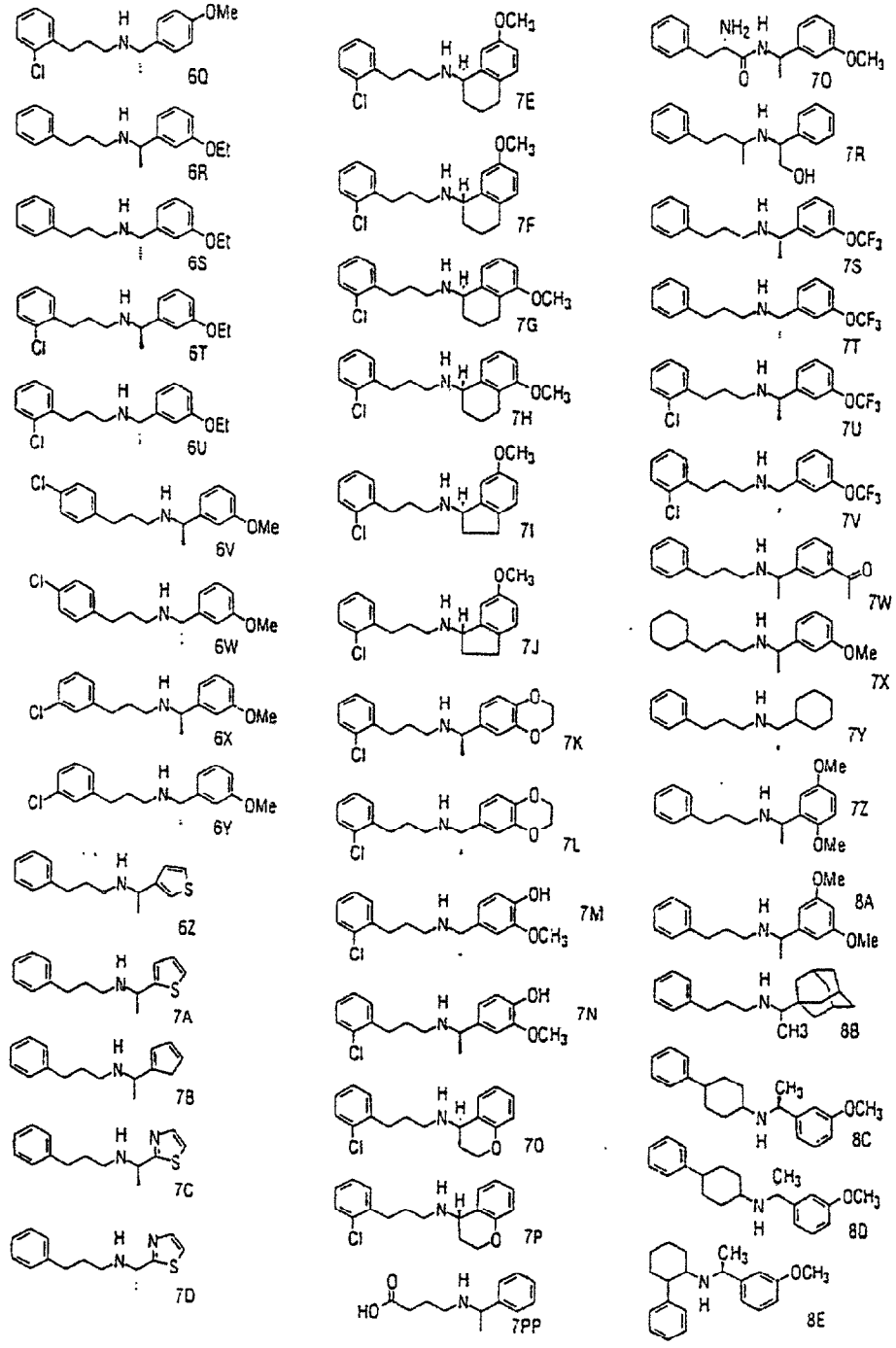
FIG. 1d.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6Z
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7F
7G
7H
7I
7J
7K
7L
7M
7N
7O
7P
7PP
7Q
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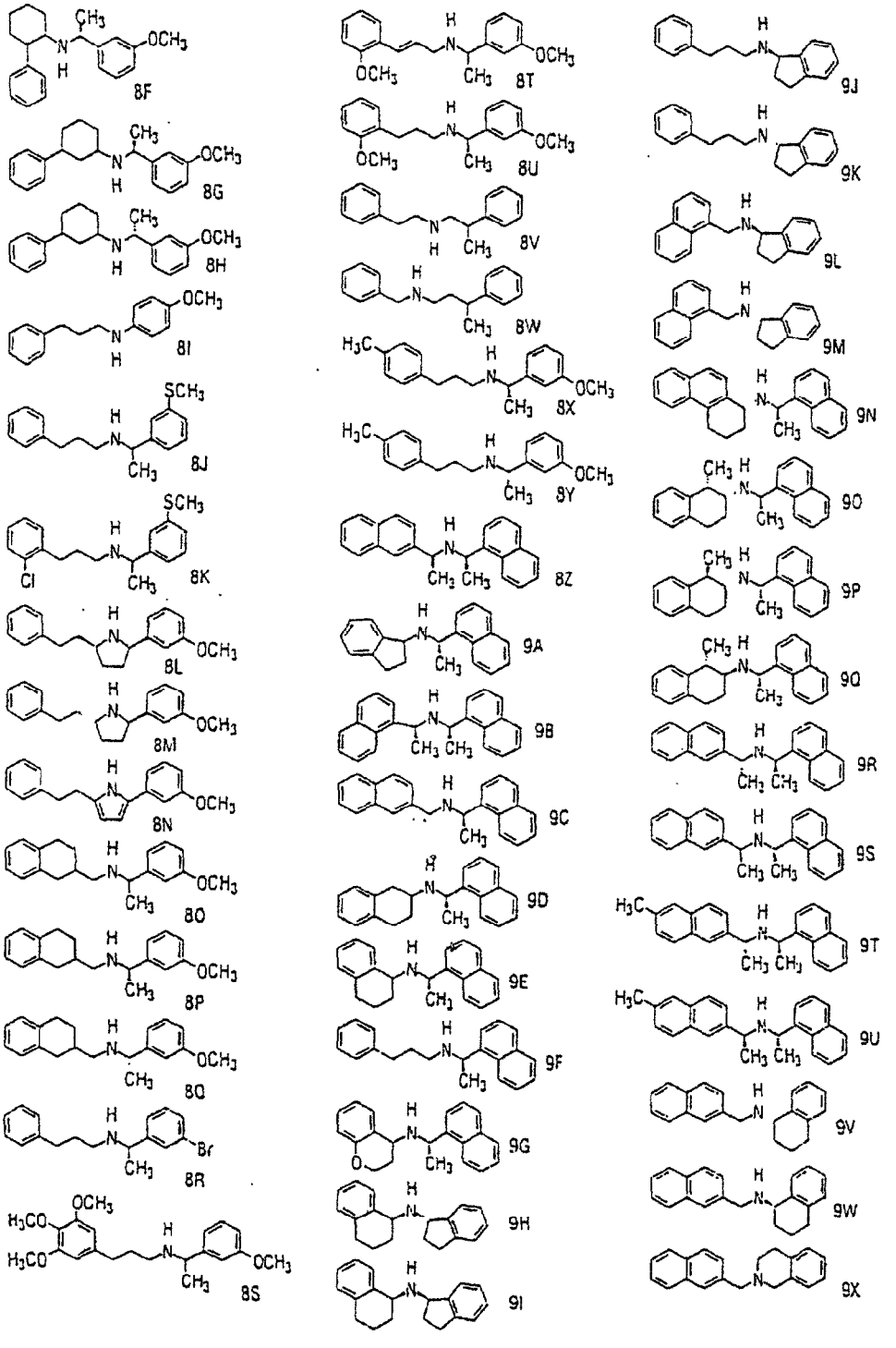
8E

FIG. 1e.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8U
8V
8W
8X
8Y
8Z
9A
9B
9C
9D
9E
9F
9G
9H
9I
9J
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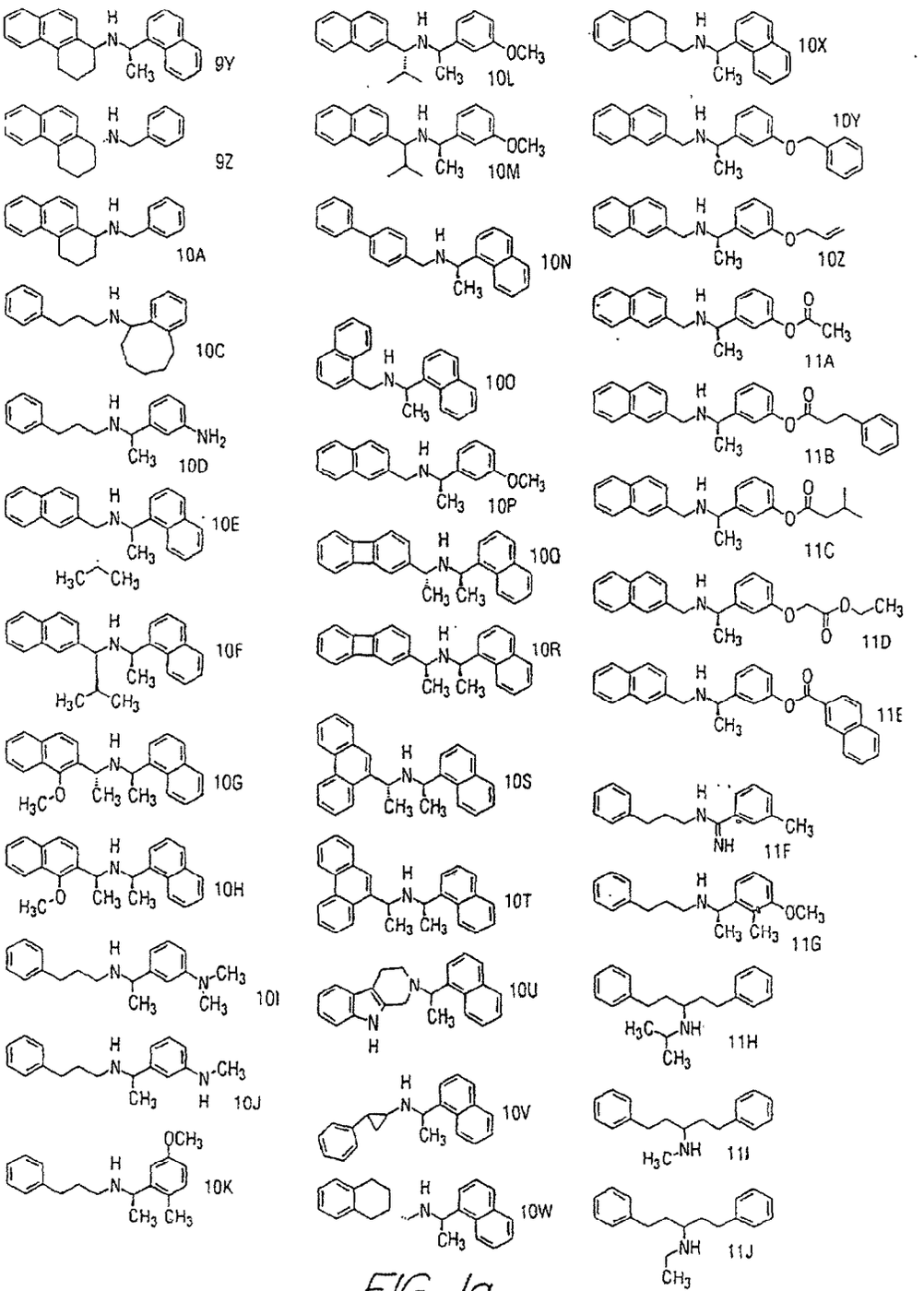
9X

FIG. 1f.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10P
10Q
10R
10S
10T
10U
10V
10W
10X
10Y
10Z
11A
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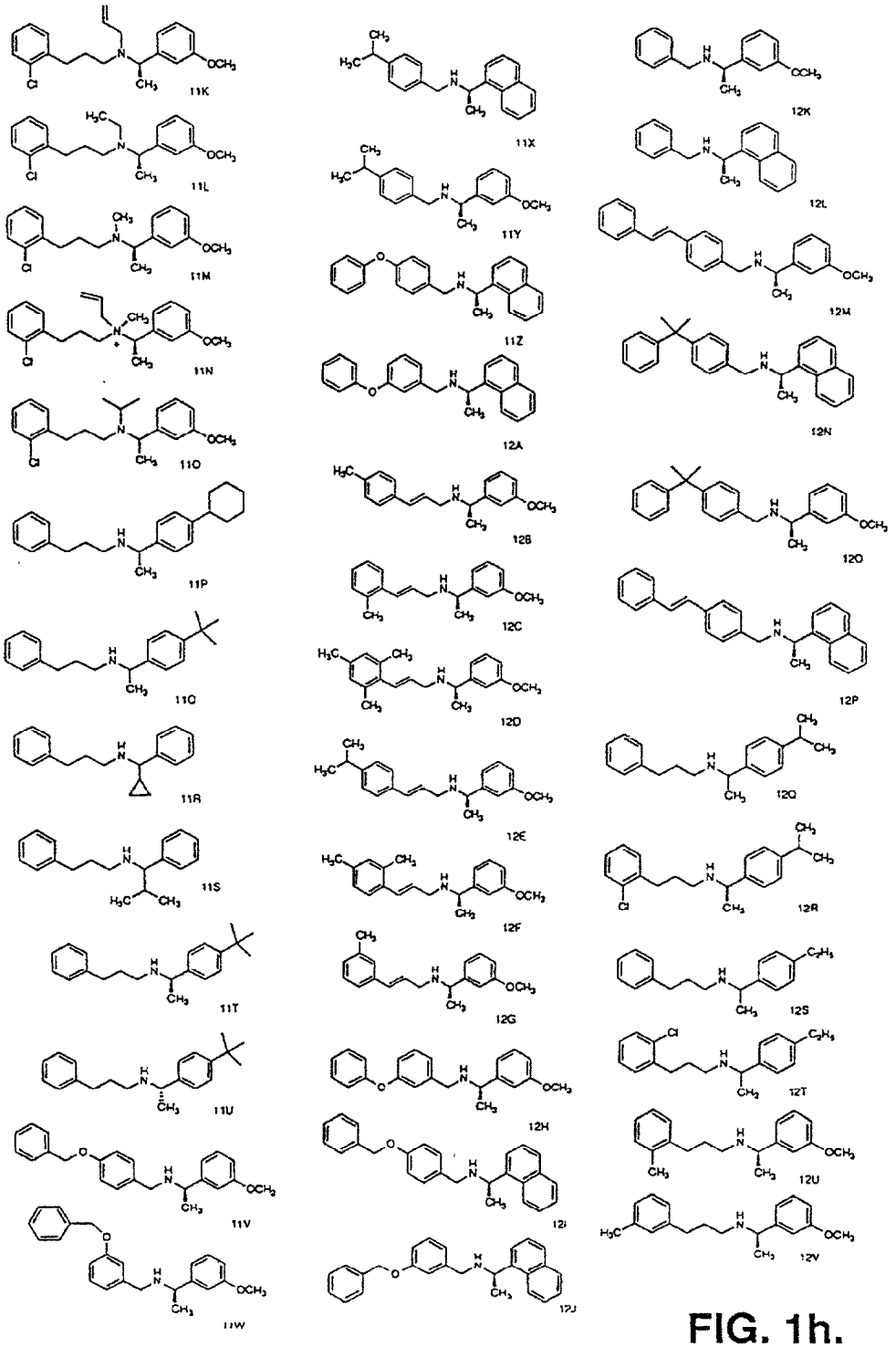
11I
11J

FIG. 1g.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12A
12B
12C
12D
12E
12F
12G
12H
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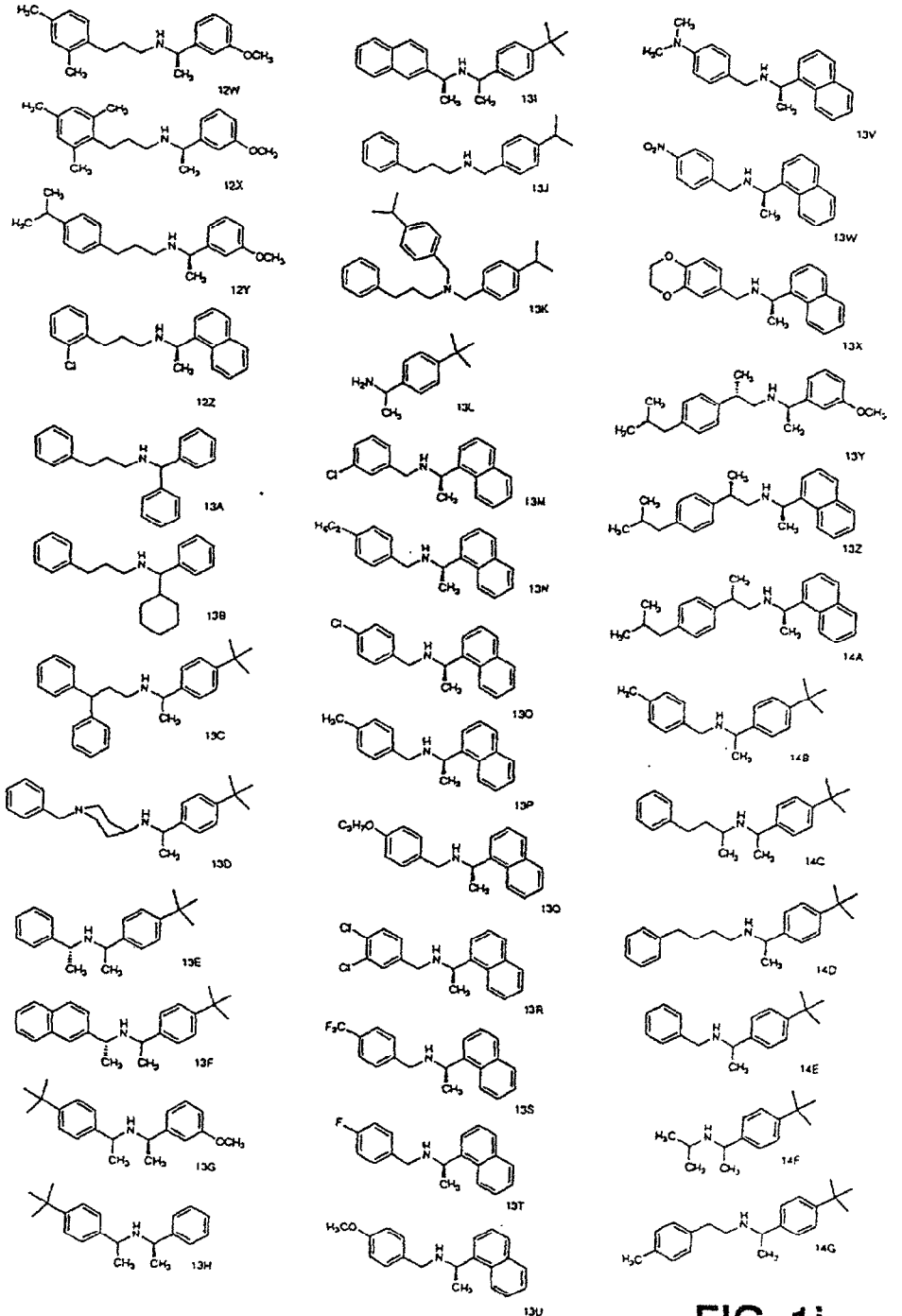
12V

FIG. 1h.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13N
13O
13P
13Q
13R
13S
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FIG. 1i.

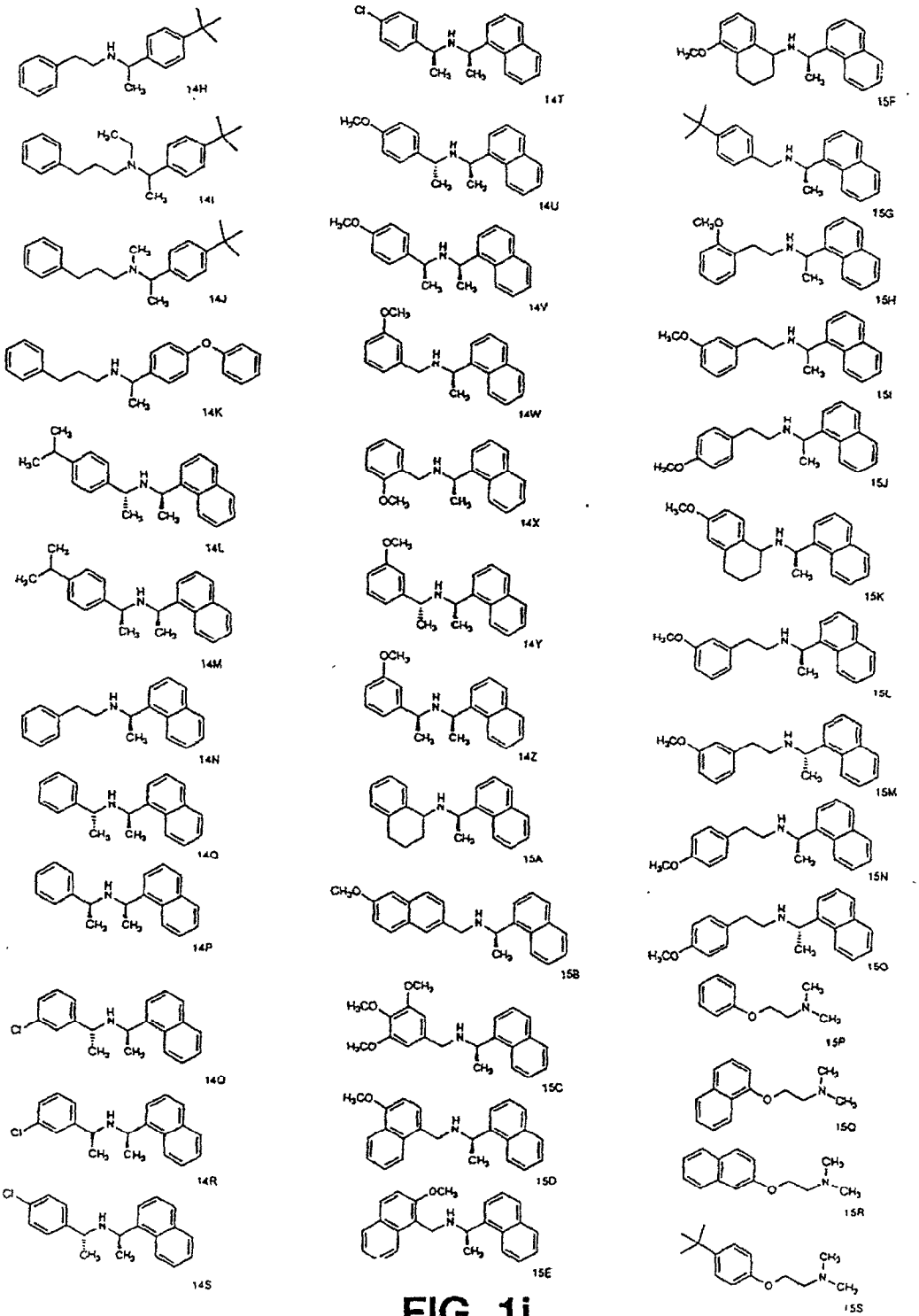
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FIG. 1j.

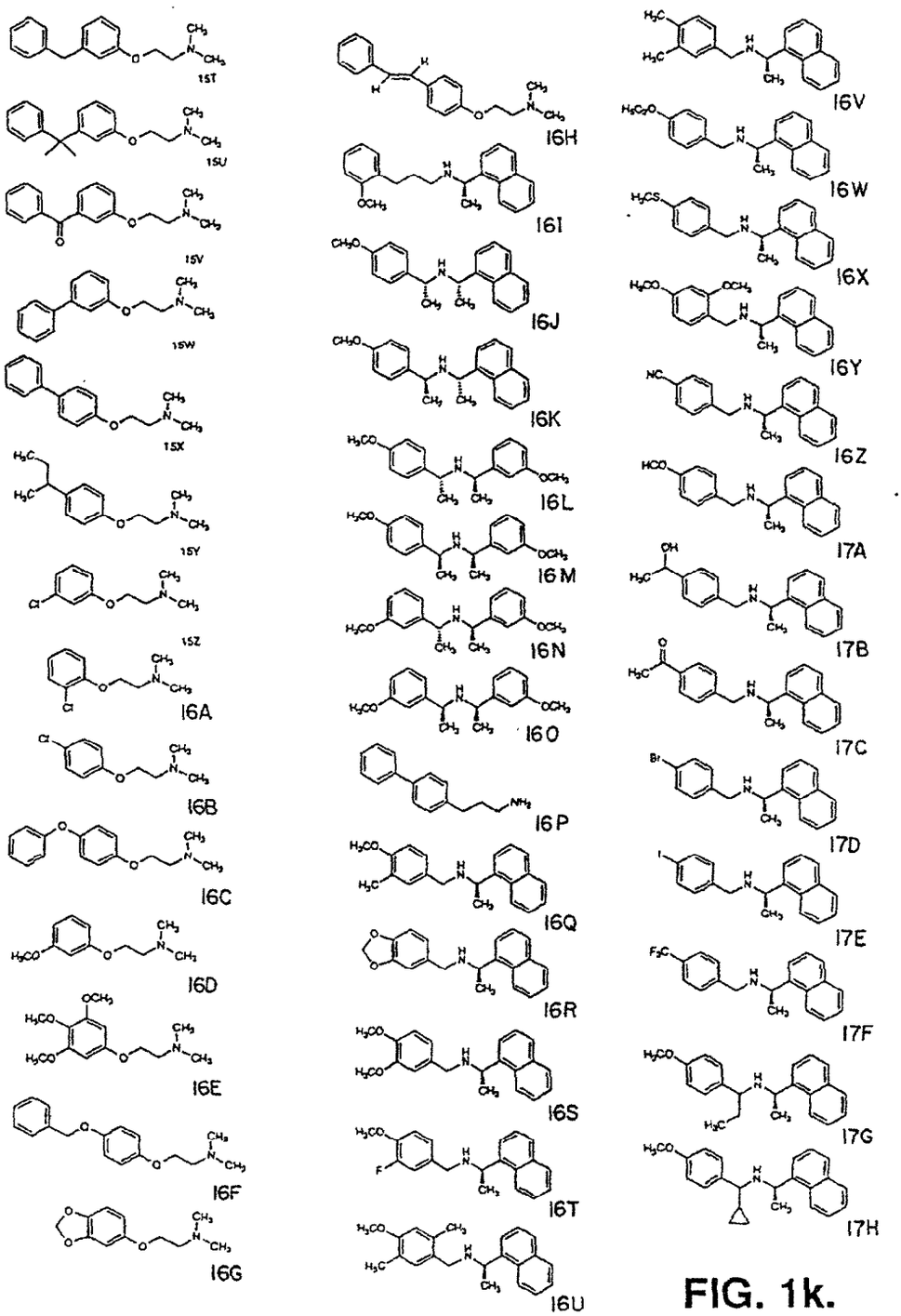
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FIG. 1k.

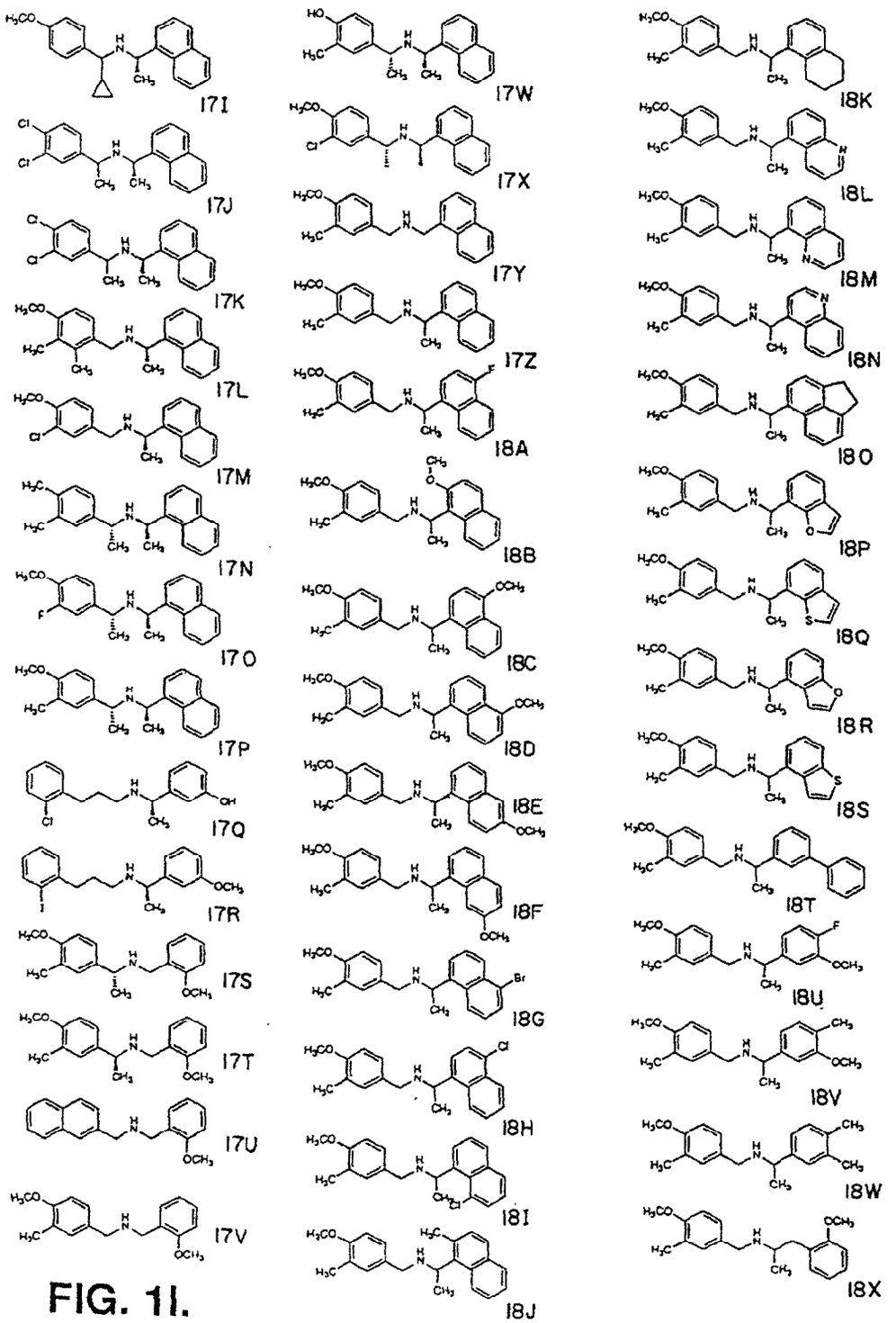
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FIG. 1I.

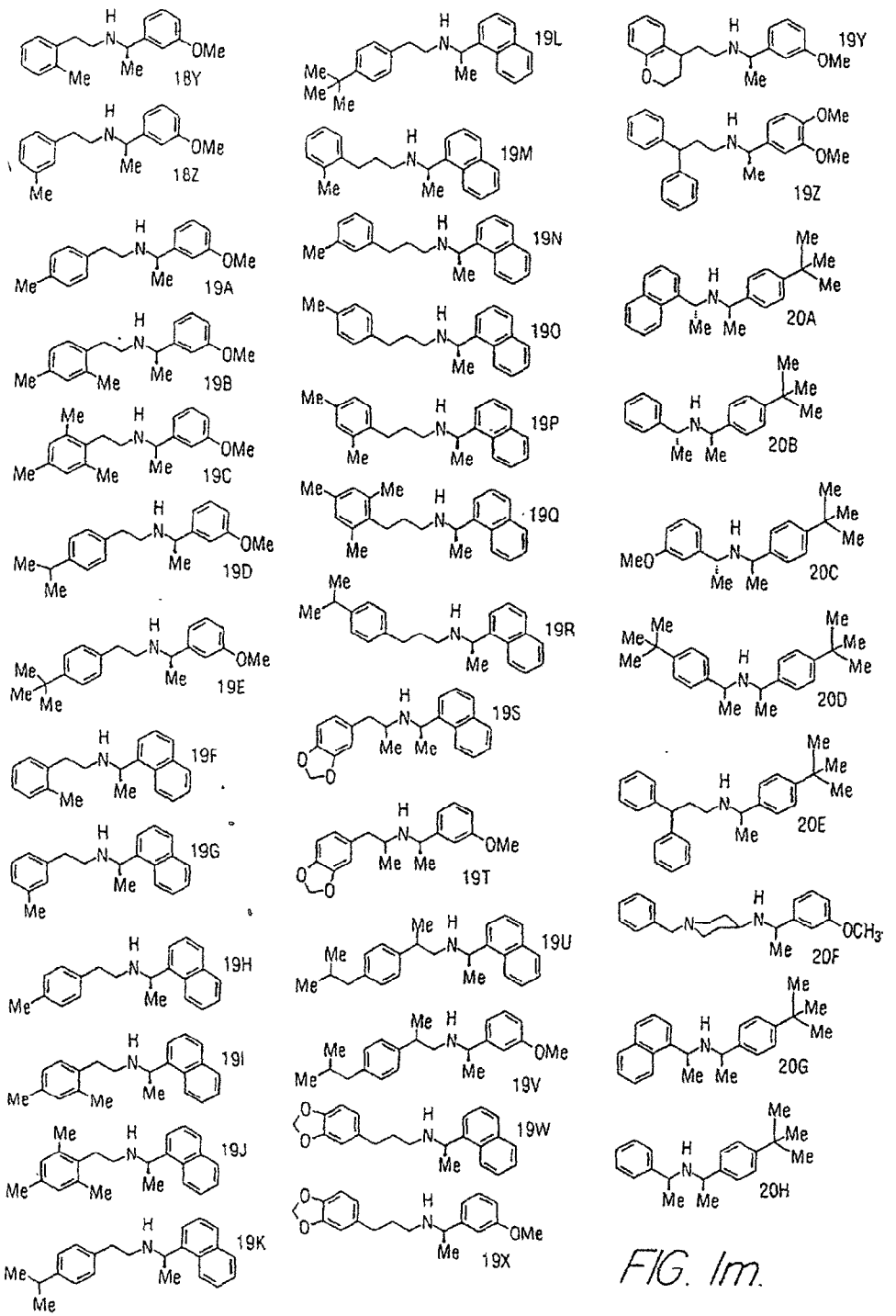
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FIG. 1m.

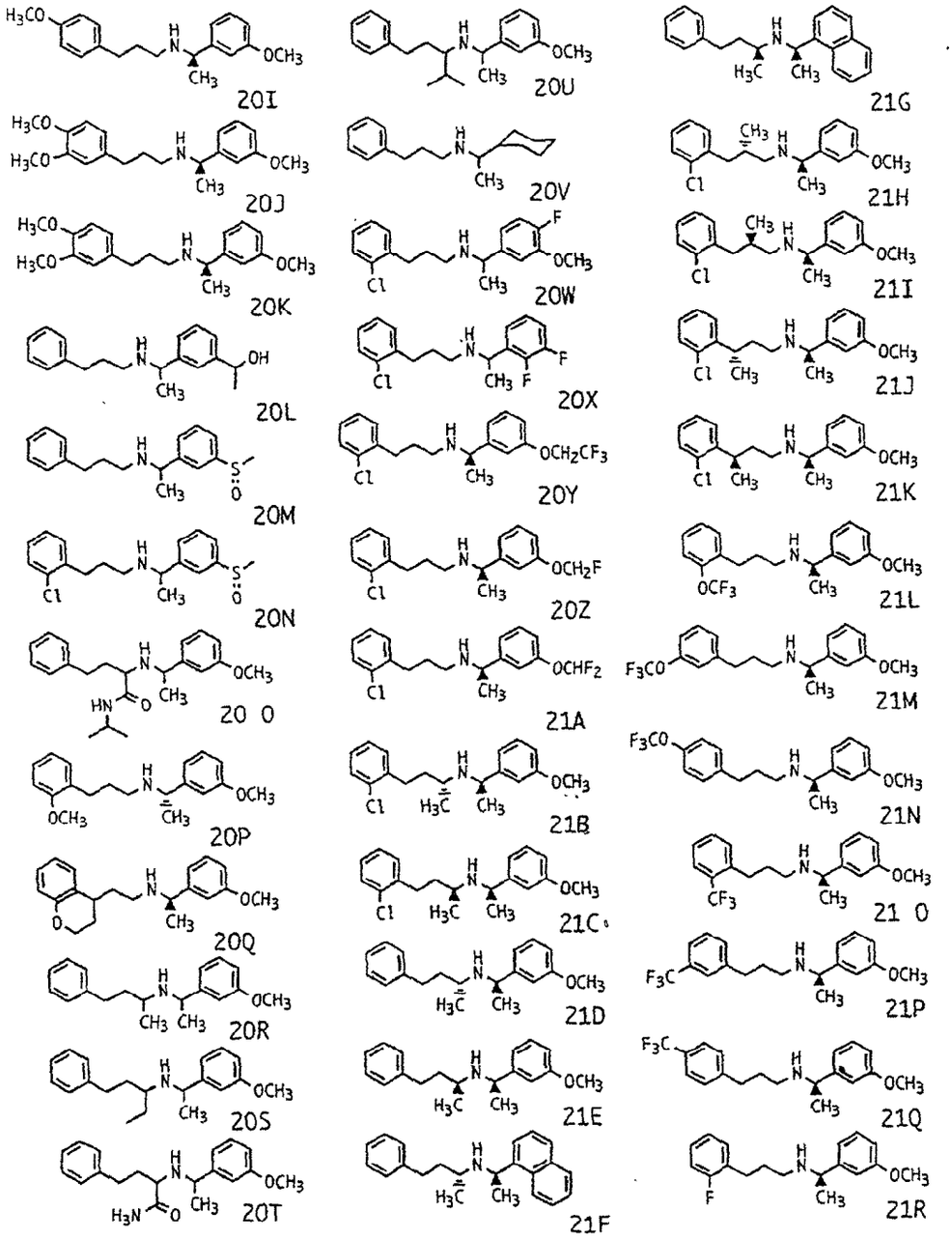
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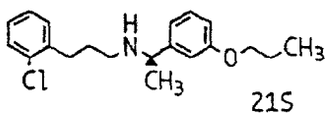
FIG. 1n.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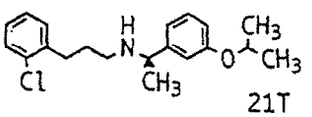
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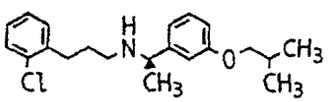
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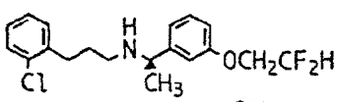
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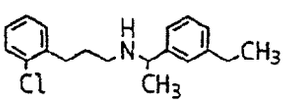
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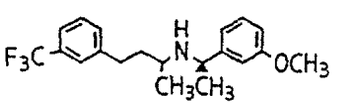
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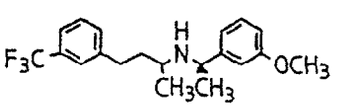
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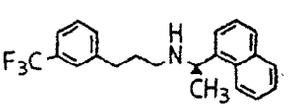
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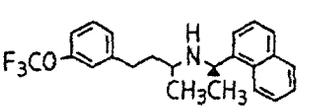
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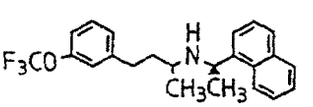
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FIG. 1o.

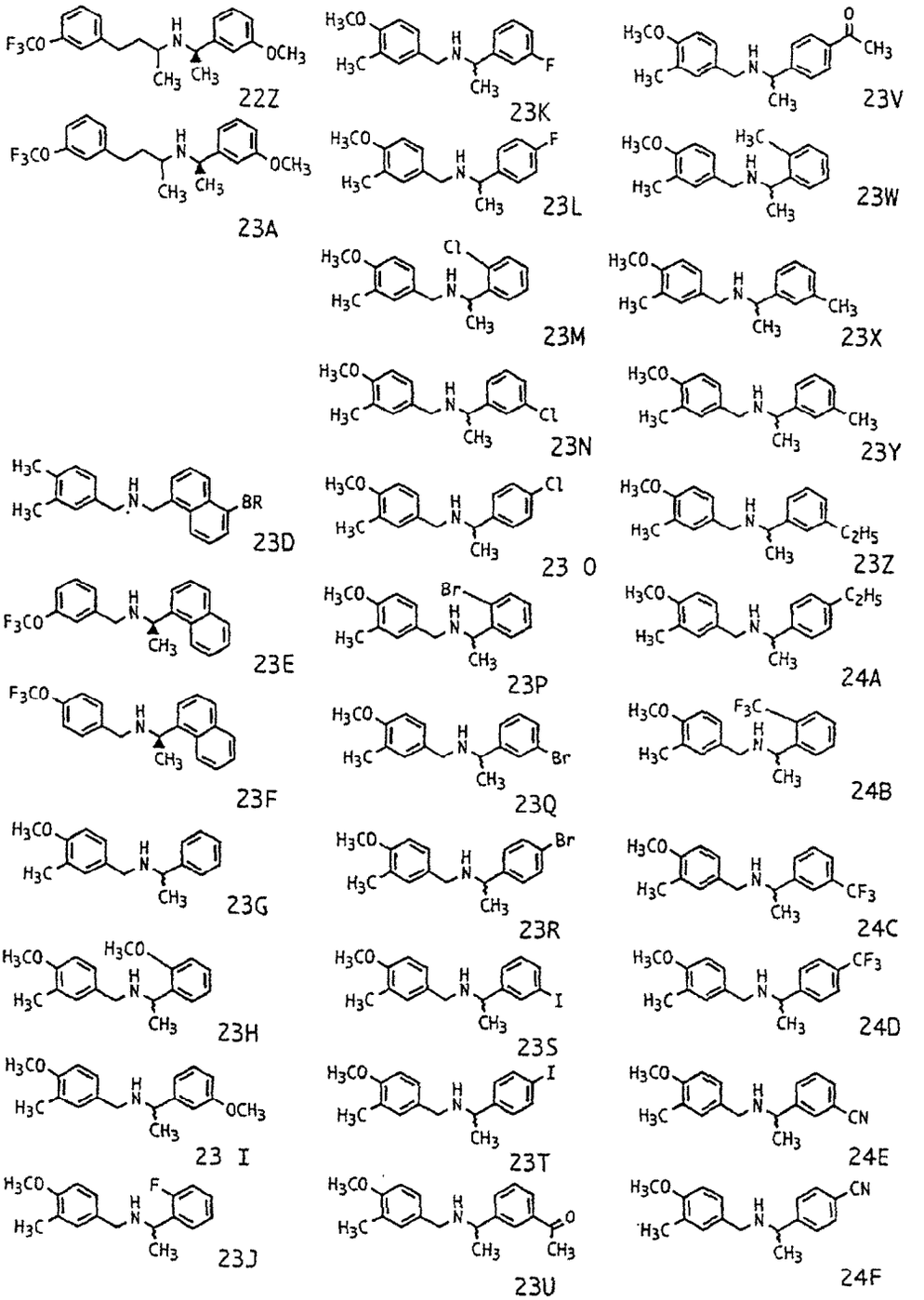
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FIG. 1p.

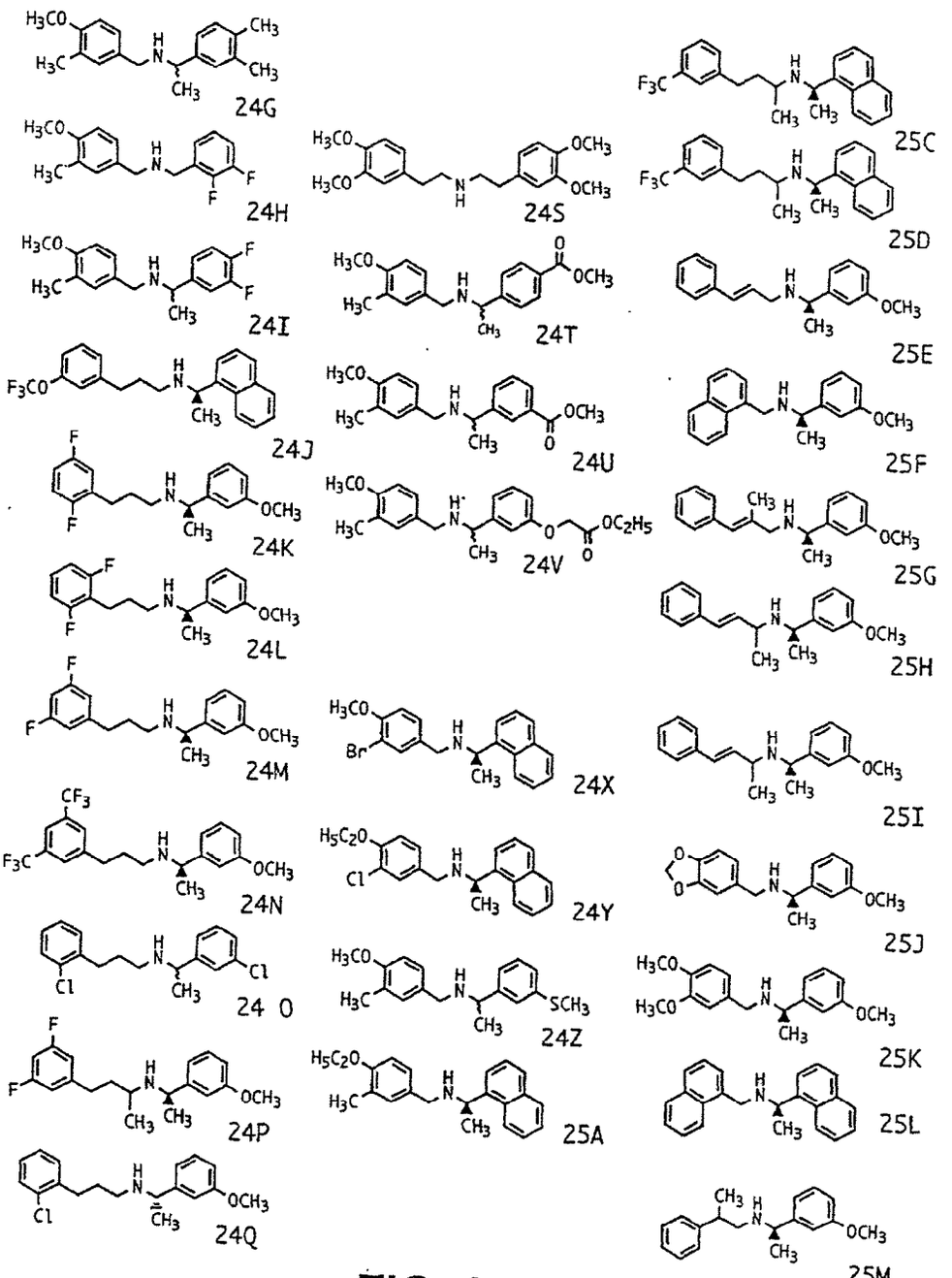
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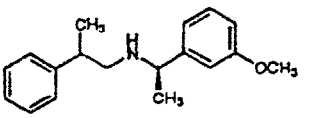
FIG. 1q.



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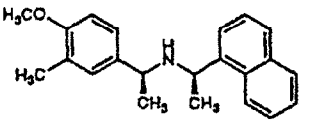

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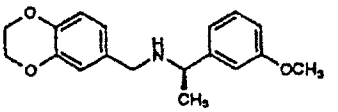

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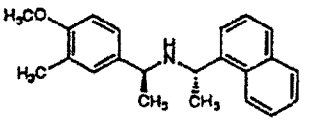

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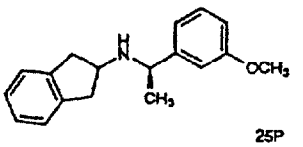

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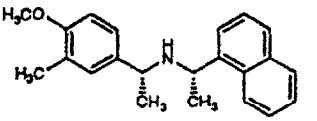

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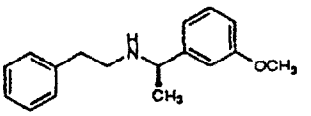

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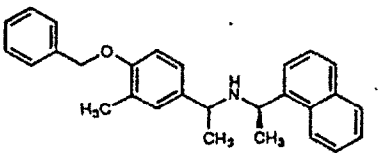
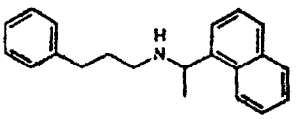
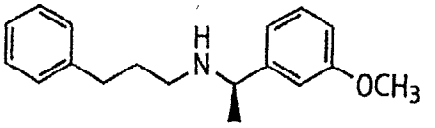


25X



25Y

FIG. 1r.

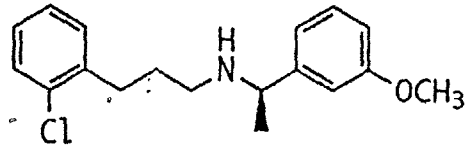


NPS *R*-467 ·HCl

mp 157.4-158 °C; $[\alpha]_D^{20}$ +41.7° (c 6.11, $CHCl_3$); UV $_{max}$ (EtOH) 276 (ε 1900), sh 282 nm (ε 1700); ^{1}H NMR ($CDCl_3$) δ 1.83 (3H, d, *J*=7, C-CH_3), 2.29 (2H, q, *J*=8), 2.51 (2H, q, *J*=6), 2.65 (2H, br m), 3.87 (3H, s, -OCH_3), 4.11 (1H, br q, CH), 6.91 (1H, dd, *J*=8, *J*=2), 7.05-7.07 (3H, m), 7.11-7.21 (3H, m), 7.27-7.32 (2H, m) 9.8 (1H, br s), 10.2 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 20.3, 27.0, 32.3, 44.9, 55.3, 58.8, 111.8, 115.3, 119.7, 125.8, 127.9 (2C), 128.1 (2C), 130.0, 137.2, 139.6, 161.1; GC/El-MS (t_R=9.03 min), *m/z* (rel. int.) 269 (M^+, 17), 254 (100), 164 (8), 135 (50), 121 (8), 105 (7), 91 (23), 77 (7); HR-El-MS observed (M^+) *m/z* 269.1796, $C_{18}H_{23}NO$ required 269.1780.

FIG. 2.

US006211244 file://\\cadmrfs01\firmdata\lp\Foley\Pat\PatentDocuments\US006211244.CPC]



NPS *R*-568 ·HCl

mp 188.188.5 °C; $[\alpha]_D^{20}$ +37.8° (c 6.80, $CHCl_3$); UV $_{max}$ (EtOH) 274 (ε 2200), sh 282 nm (ε 1900); ^{1}H NMR ($CDCl_3$) δ 1.85 (3H, d, *J*=7, C-CH_3), 2.24 (2H, q, *J*=8), 2.66 (2H, q, *J*=7), 2.68 (2H, br q, *J*=7), 3.87 (3H, s, -OCH_3), 4.15 (1H, br t, J=7, CH), 6.90 (1H, dd, *J*=8, *J*=2), 7.06-7.15 (4H, m), 7.23-7.32 (3H, m), 9.85 (1H, br s), 10.2 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 20.2, 25.2, 30.0, 44.7, 55.6, 58.6, 112.0, 115.3, 119.7, 126.5, 127.4, 129.1, 129.9, 130.0, 133.4, 137.1, 137.2, 160.0; GC/El-MS (t_R=9.93 min), *m/z* (rel. int.) 303 (M^+,2), 288 (100), 268 (17), 196 (4), 164 (8), 135 (56), 126 (21), 103 (9); 91 (7), 77 (7); HR-El-MS observed (M^+) *m/z* 303.1403, $C_{18}H_{22}ClNO$ required 303.1390.

FIG. 3.

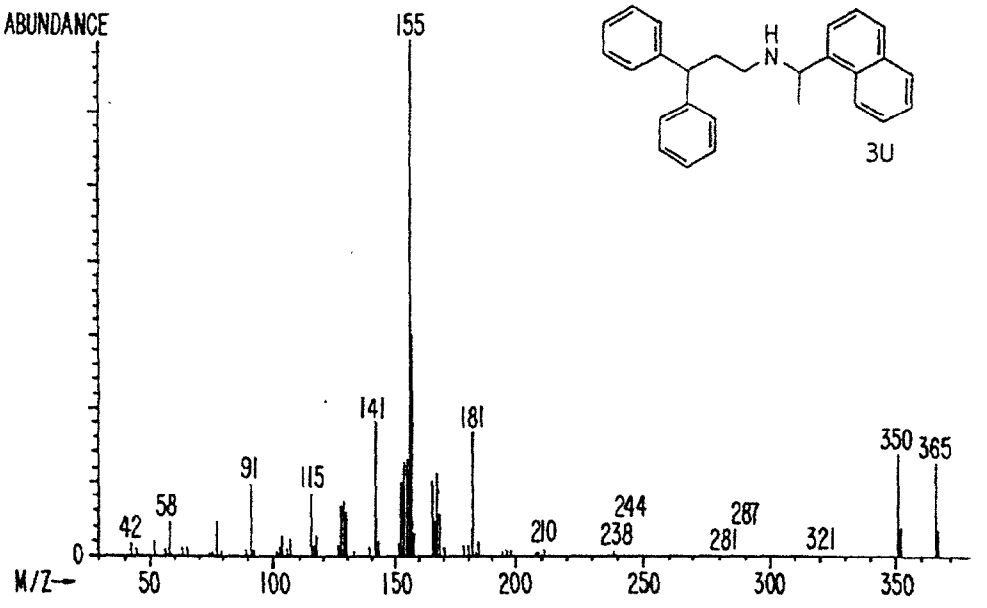

ABUNDANCE
155
141
181
91
115
58
42
210
244
238
287
281
321
350
365
0
M/Z
50
100
150
200
250
300
350
H
N
3U

FIG. 4.

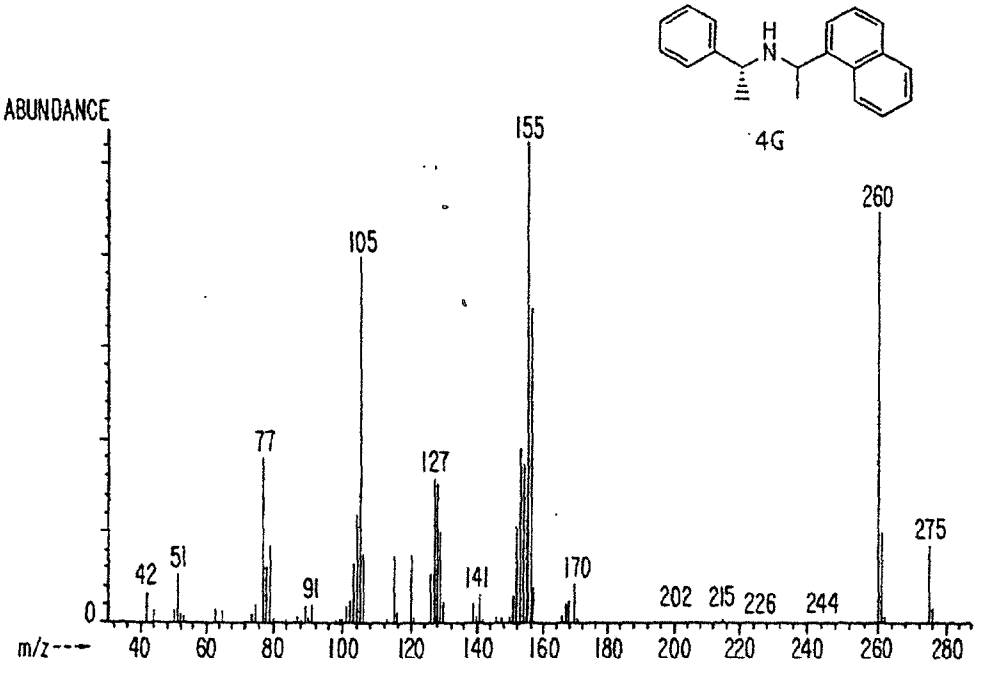

ABUNDANCE
155
105
77
127
42
51
91
141
170
202
215
226
244
260
275
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
H
N
4G

FIG. 5.

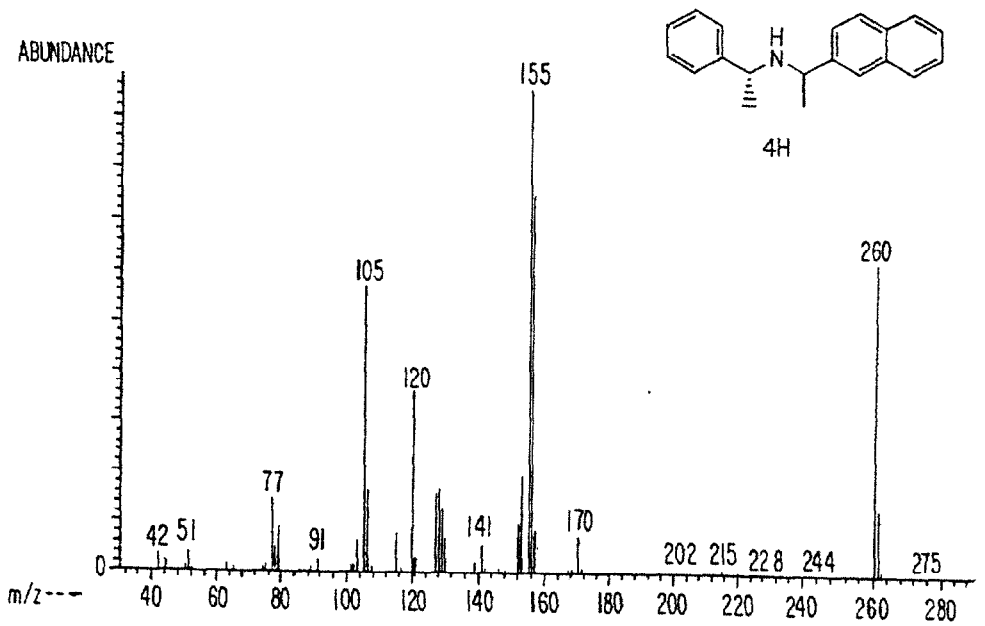

ABUNDANCE
155
105
120
77
42 51
91
141
170
202 215 228 244
260
275
0
m/z---
40 60 80 100 120 140 160 180 200 220 240 260 280
H
N
4H

FIG. 6.

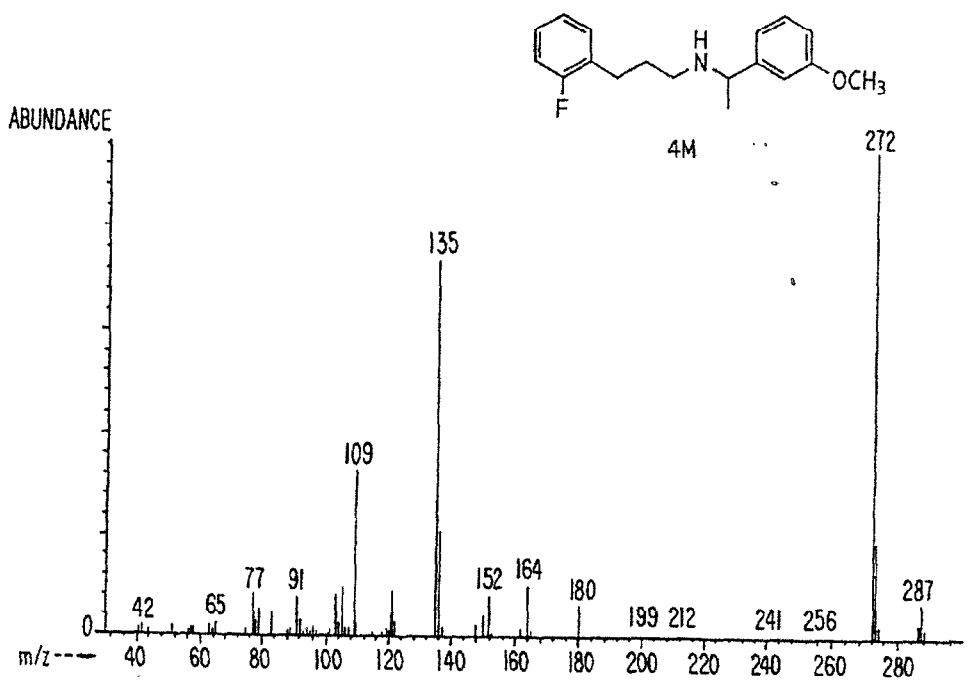

ABUNDANCE
135
109
77 91
42
65
152 164
180
199 212
241 256
272
287
0
m/z---
40 60 80 100 120 140 160 180 200 220 240 260 280
H
N
F
OCH3
4M

FIG. 7.

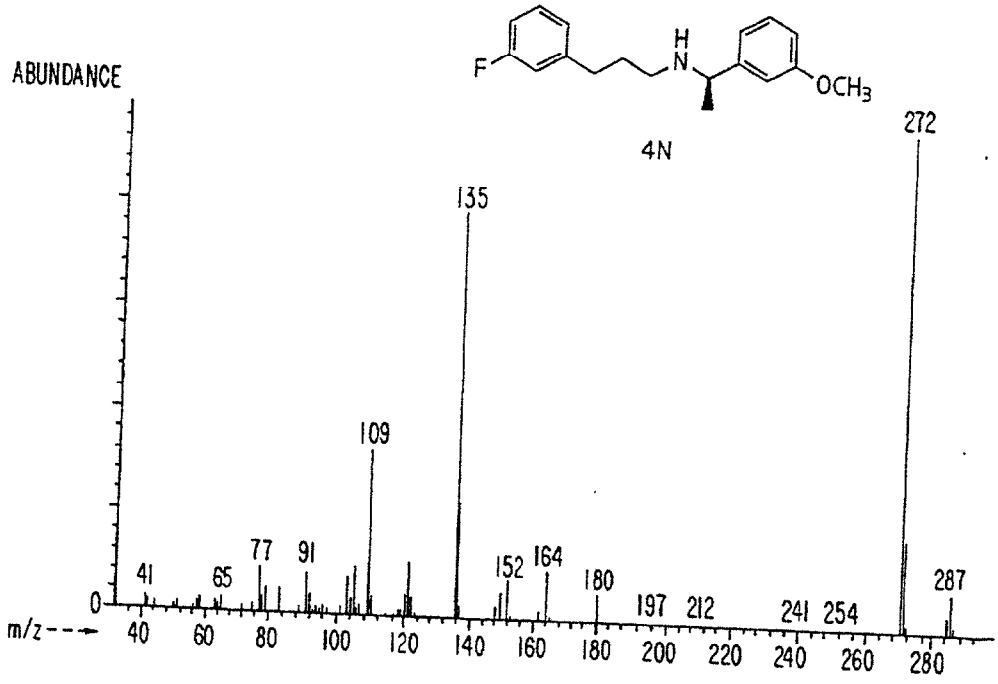

ABUNDANCE
F
H
N
OCH3
4N
272
135
109
77
91
41
65
152
164
180
197
212
241
254
287
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 8.

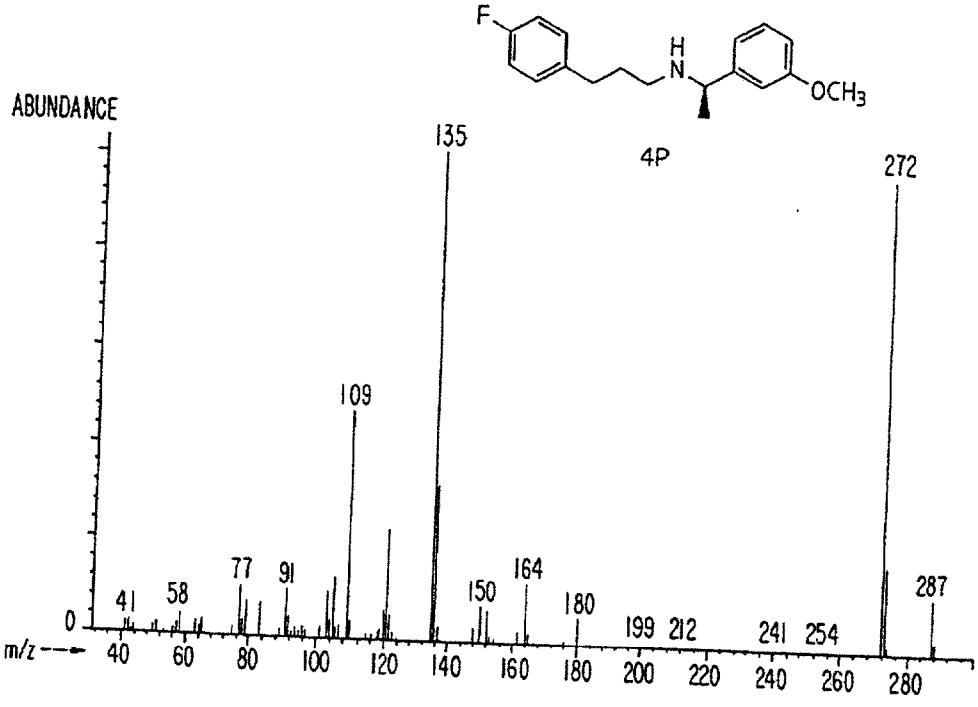
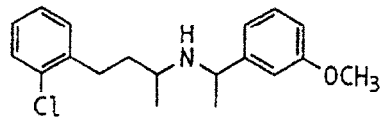

ABUNDANCE
F
H
N
OCH3
4P
135
272
109
77
91
41
58
150
164
180
199
212
241
254
287
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 9.


H
N
OCH3
Cl

4T

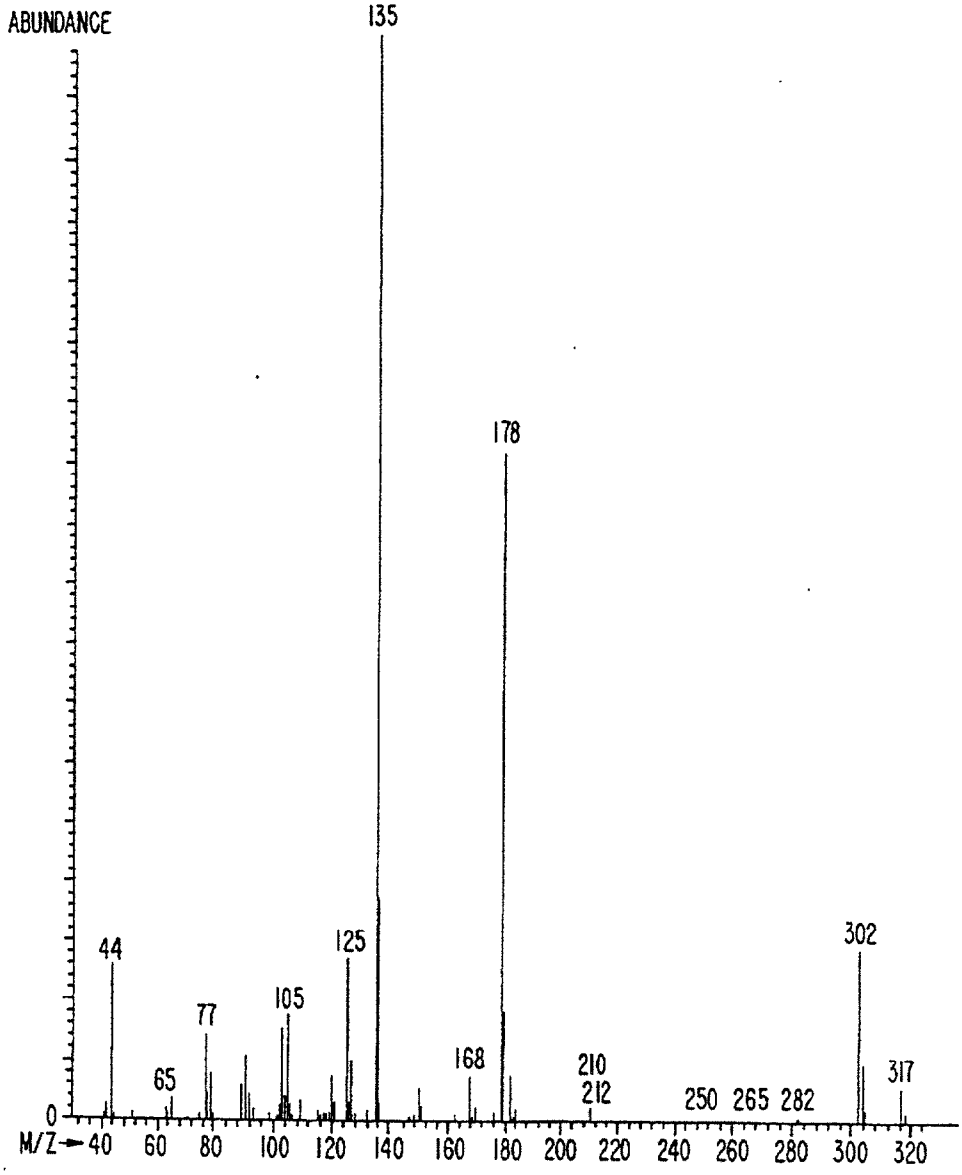

ABUNDANCE
135
178
44
125
302
77
105
65
168
210
212
250 265 282
317
0
M/Z→40 60 80 100 120 140 160 180 200 220 240 260 280 300 320

FIG. 10.

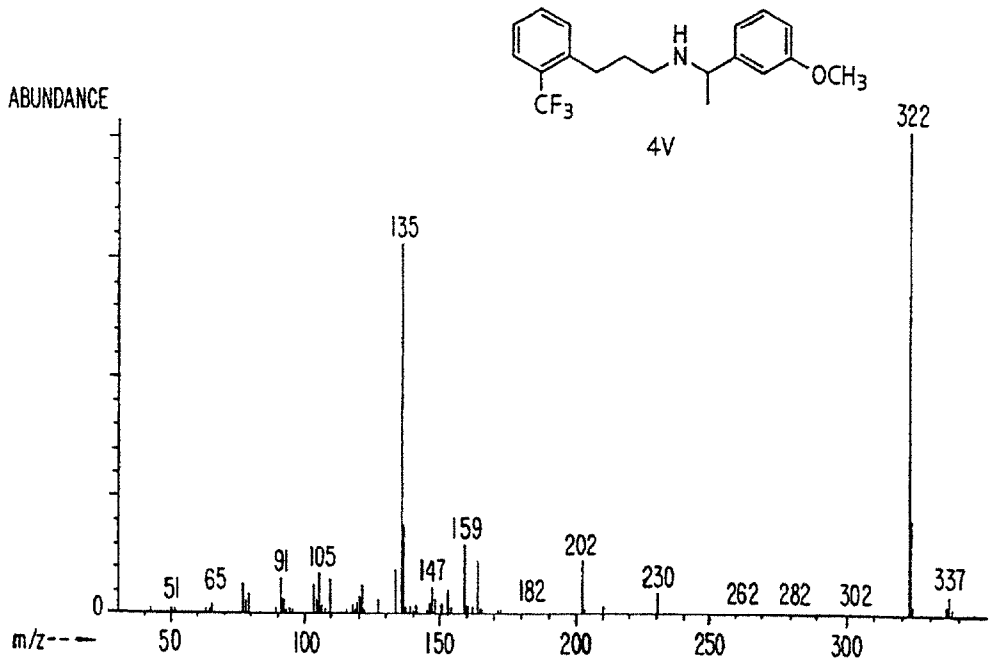

ABUNDANCE
H
N
OCH3
CF3
4V
322
135
159
202
91
105
147
51
65
182
230
262
282
302
337
0
m/z--
50
100
150
200
250
300

FIG. 11.

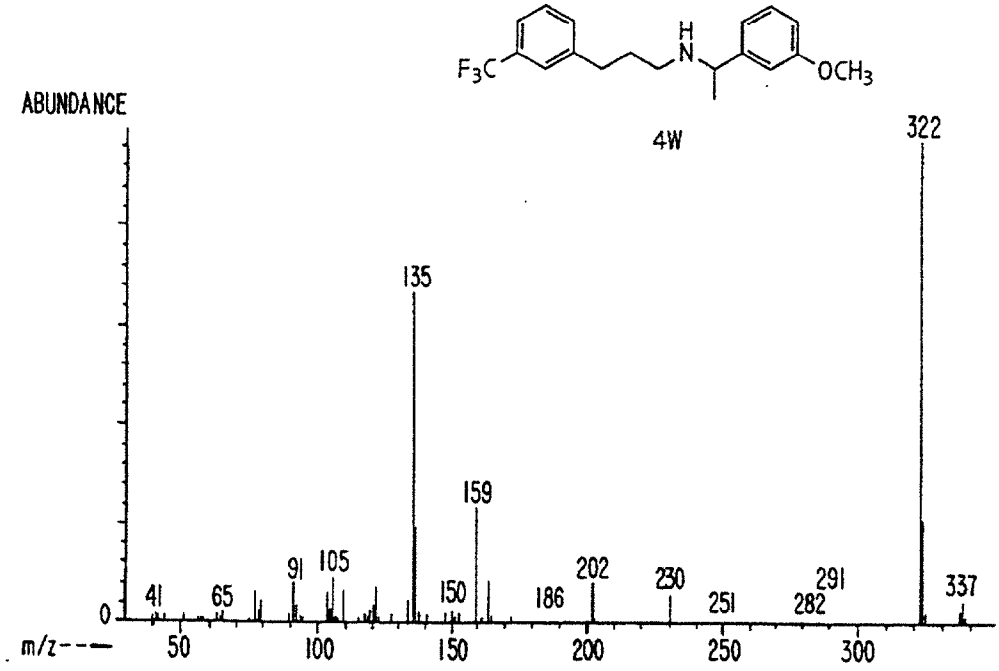

ABUNDANCE
H
N
F3C
OCH3
4W
322
135
159
91
105
202
230
291
41
65
150
186
251
282
337
0
m/z--
50
100
150
200
250
300

FIG. 12.

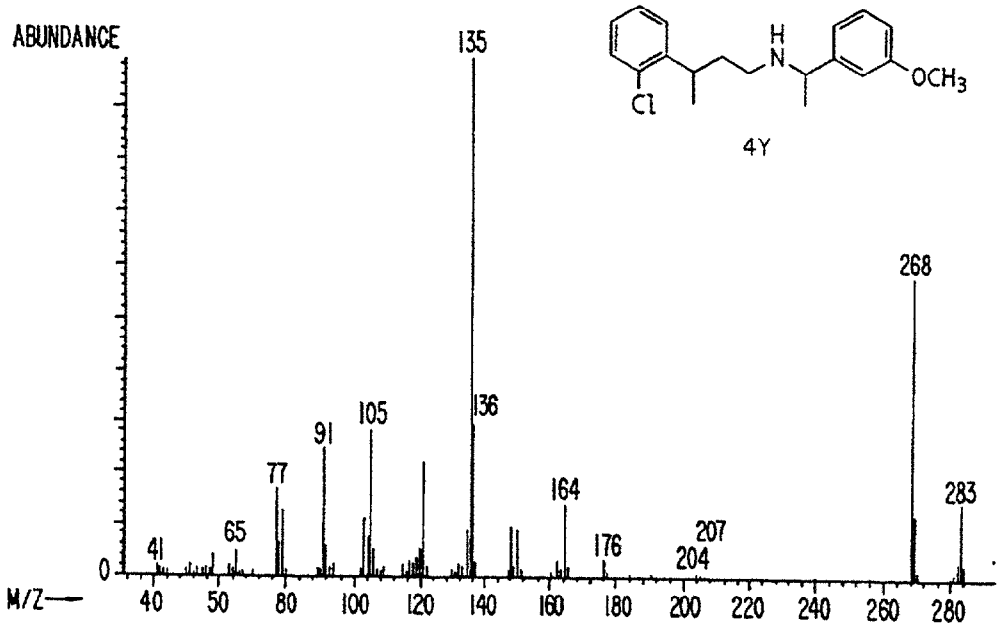

ABUNDANCE
135
268
136
105
91
77
164
283
65
41
176
207
204
0
M/Z
40
50
80
100
120
140
160
180
200
220
240
260
280
Cl
H
N
OCH3
4Y

FIG. 13.

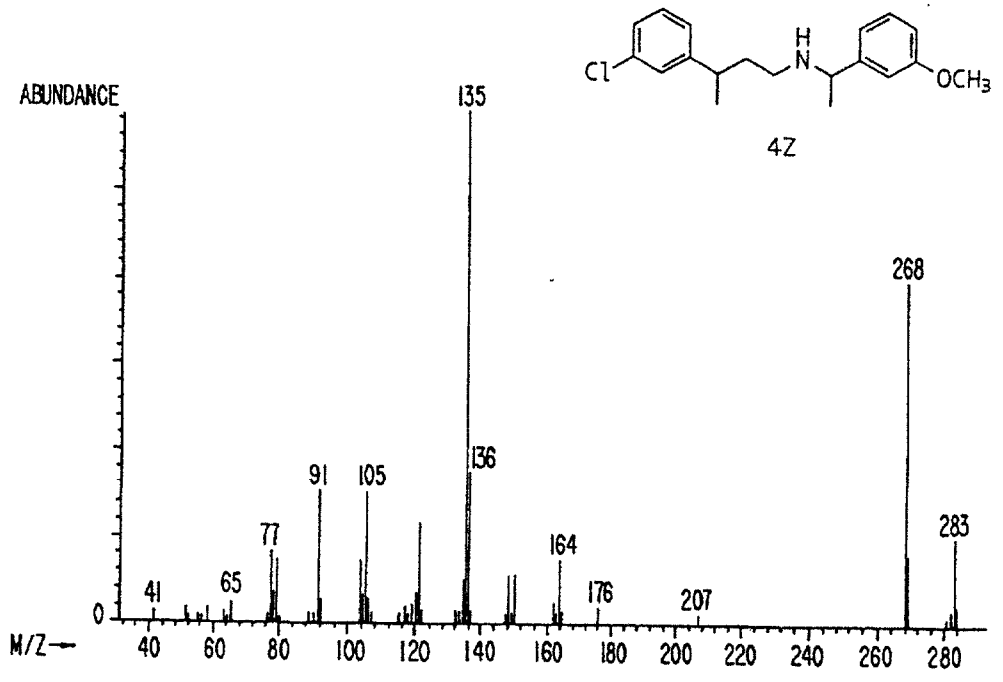

ABUNDANCE
135
268
136
91
105
77
164
283
41
65
176
207
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
Cl
H
N
OCH3
4Z

FIG. 14.

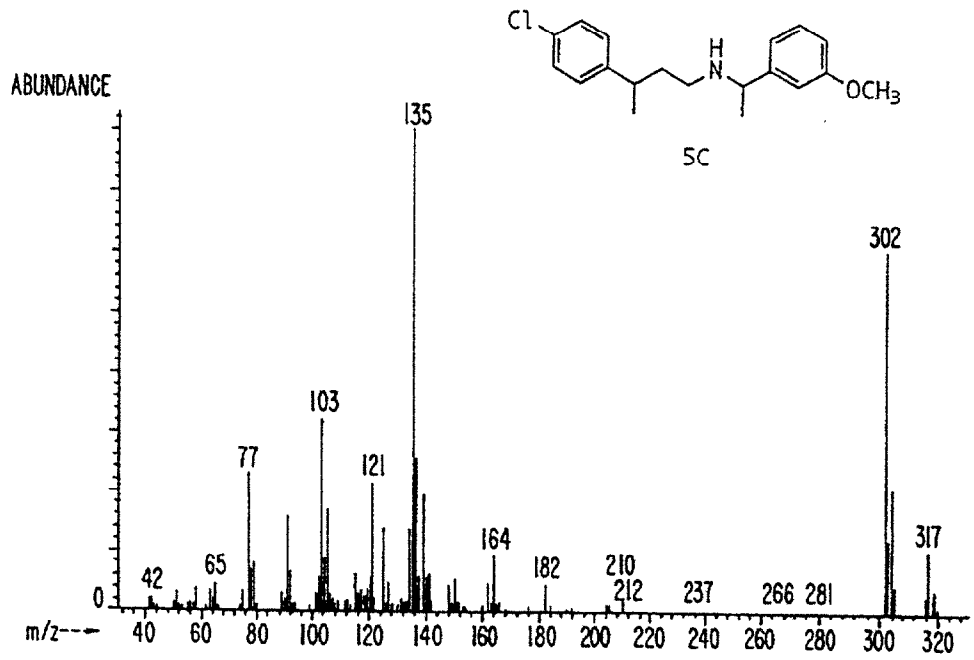

ABUNDANCE
Cl
H
N
OCH3
5C
135
302
103
77
121
164
317
42
65
182
210
212
237
266
281
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320

FIG. 15.

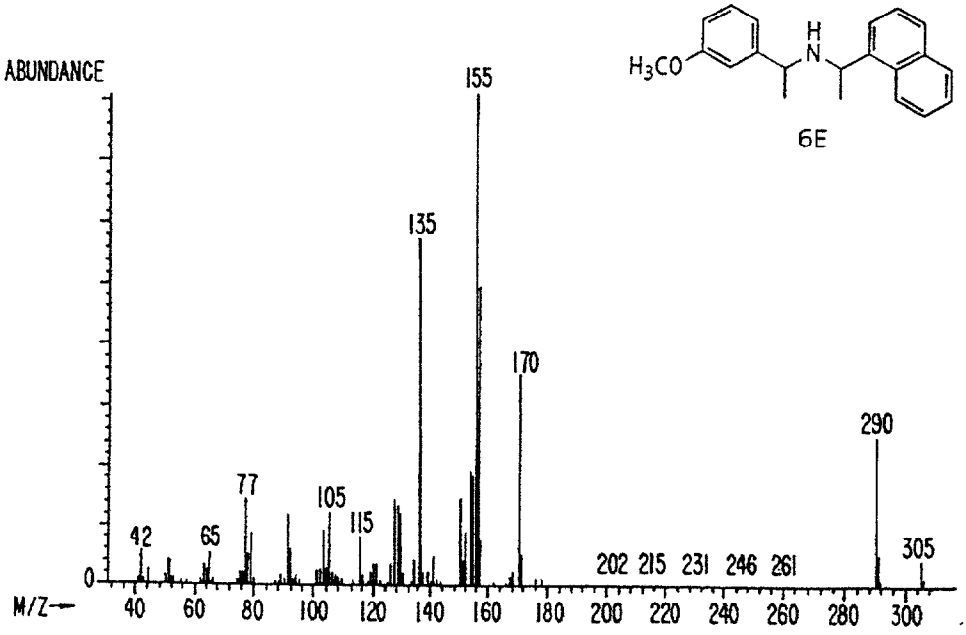

ABUNDANCE
H3CO
H
N
6E
155
135
170
290
77
105
115
42
65
202
215
231
246
261
305
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 16.

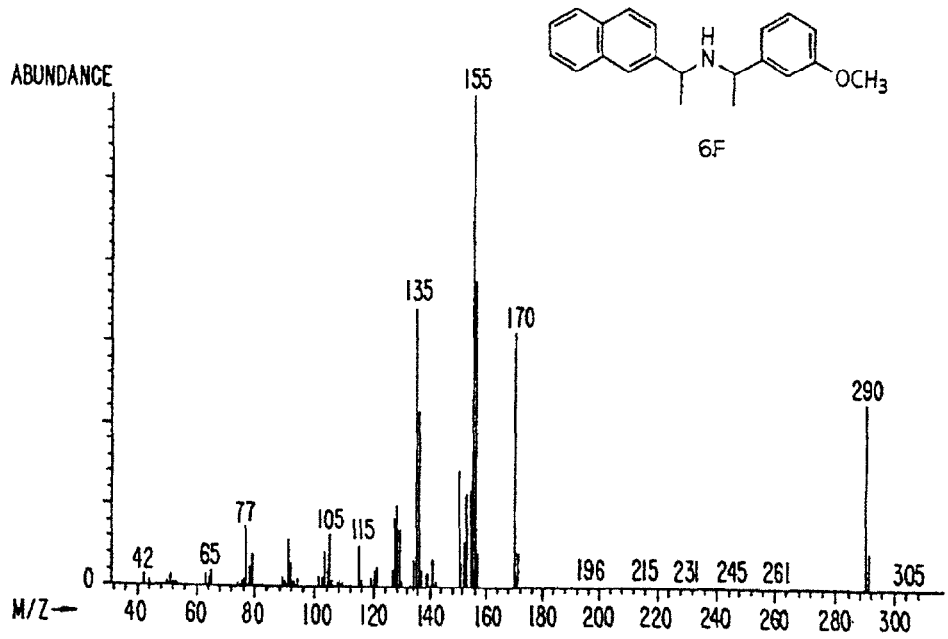

ABUNDANCE
155
135
170
290
77
105
115
42
65
196
215
231
245
261
305
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
H
N
OCH3
6F

FIG. 17.

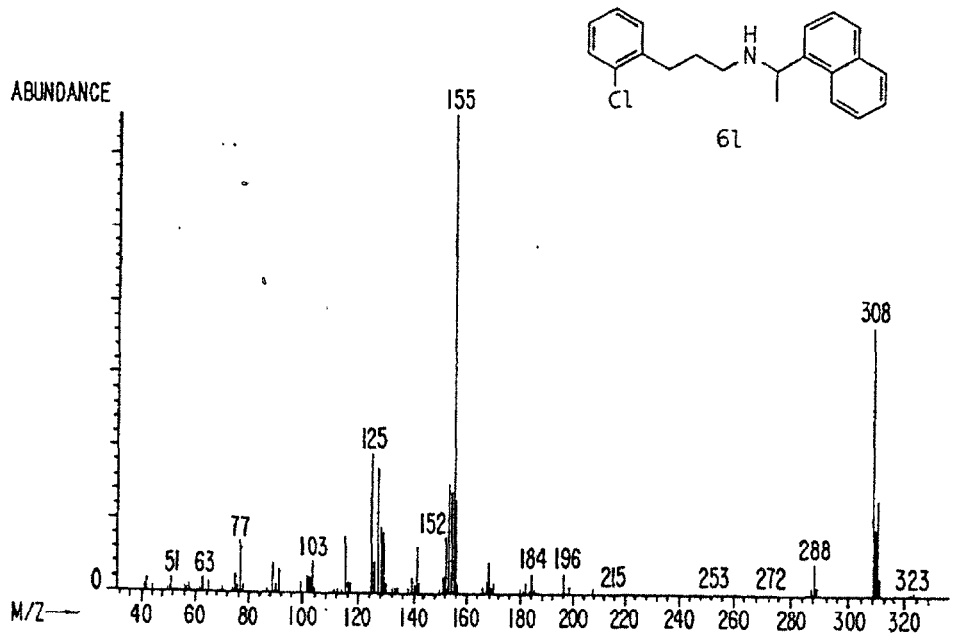

ABUNDANCE
155
308
125
77
152
103
51
63
184
196
215
253
272
288
323
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
H
N
Cl
6l

FIG. 18.

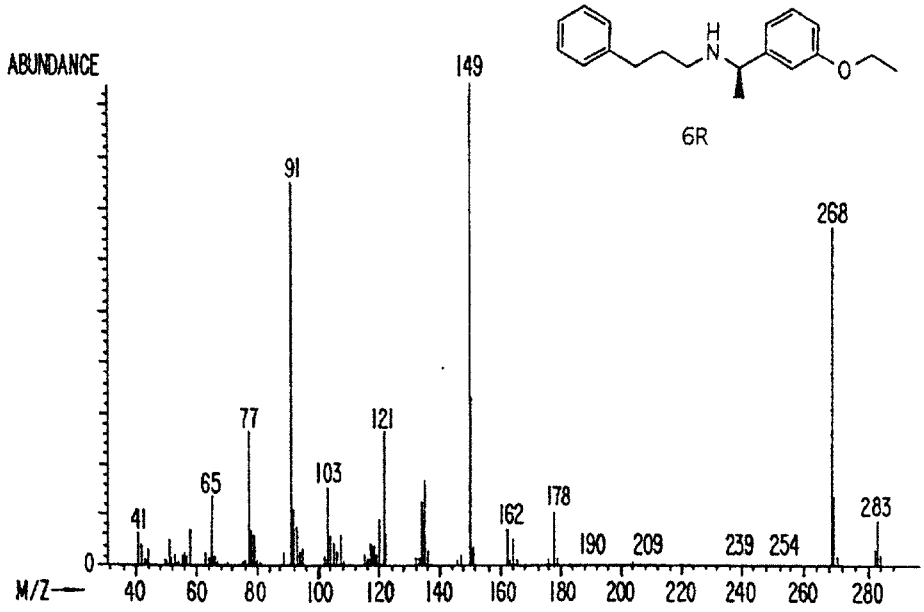

ABUNDANCE
6R
149
91
268
77
121
65
103
41
162
178
283
190
209
239
254
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 19.

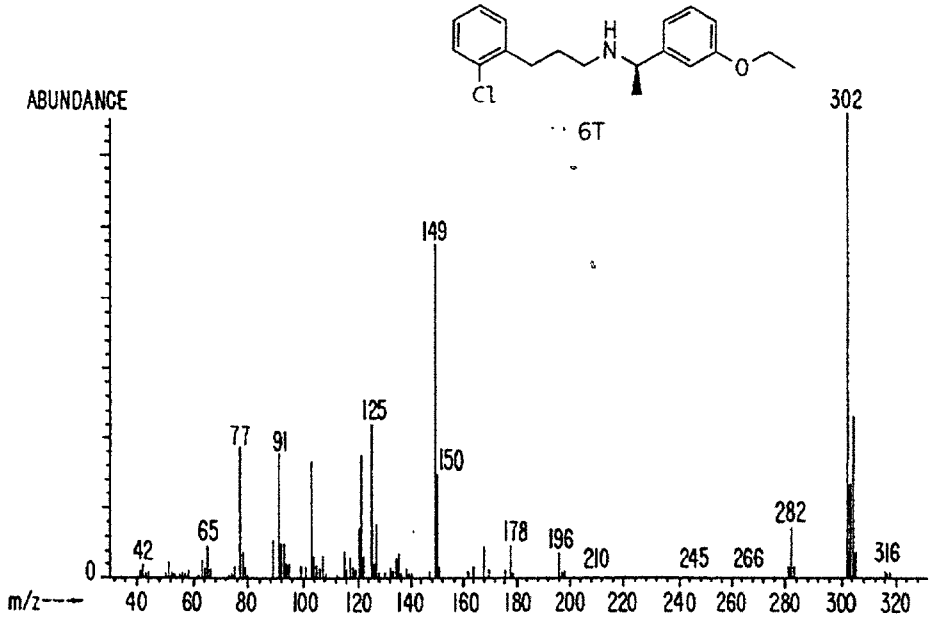

ABUNDANCE
6T
302
149
125
77
91
150
282
65
42
178
196
210
245
266
316
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320

FIG. 20.

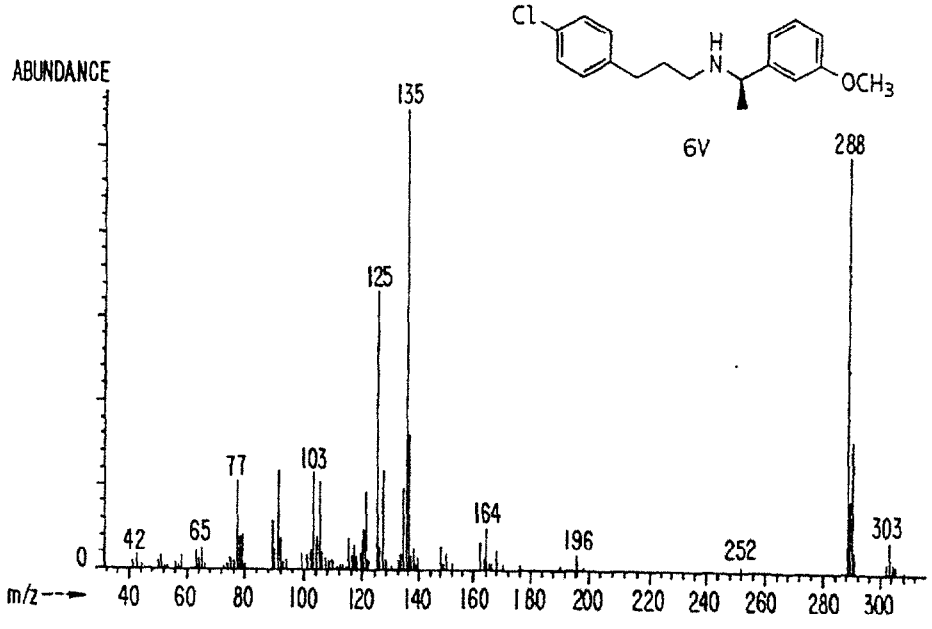

ABUNDANCE
Cl
H
N
OCH3
6V
135
288
125
77
103
164
42
65
196
252
303
0
m/z
40 60 80 100 120 140 160 180 200 220 240 260 280 300

FIG. 21.

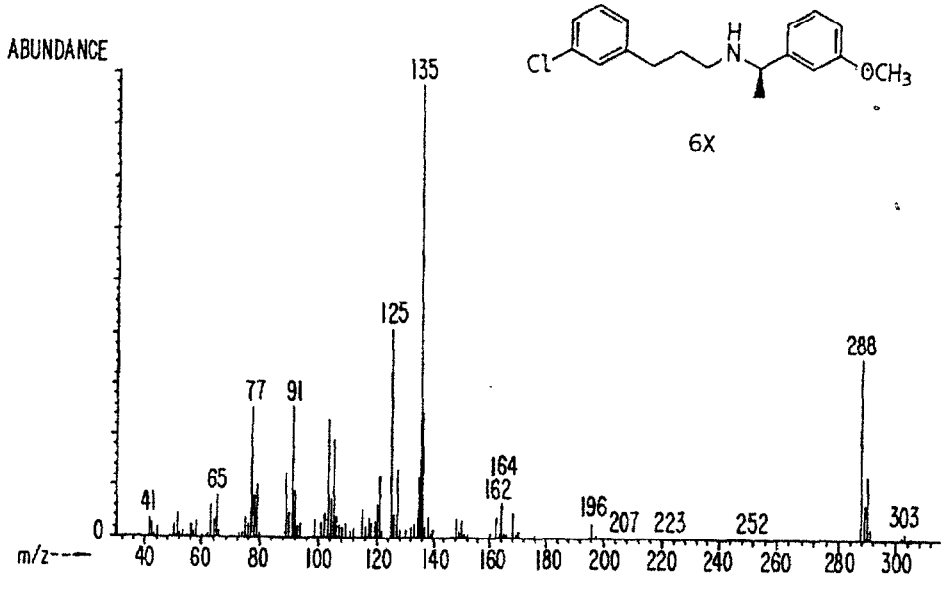
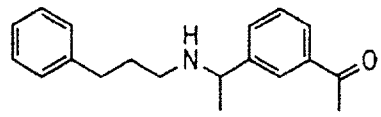

ABUNDANCE
Cl
H
N
OCH3
6X
135
125
288
77
91
65
164
162
41
196
207
223
252
303
0
m/z
40 60 80 100 120 140 160 180 200 220 240 260 280 300

FIG. 22.


H
N
O

7W

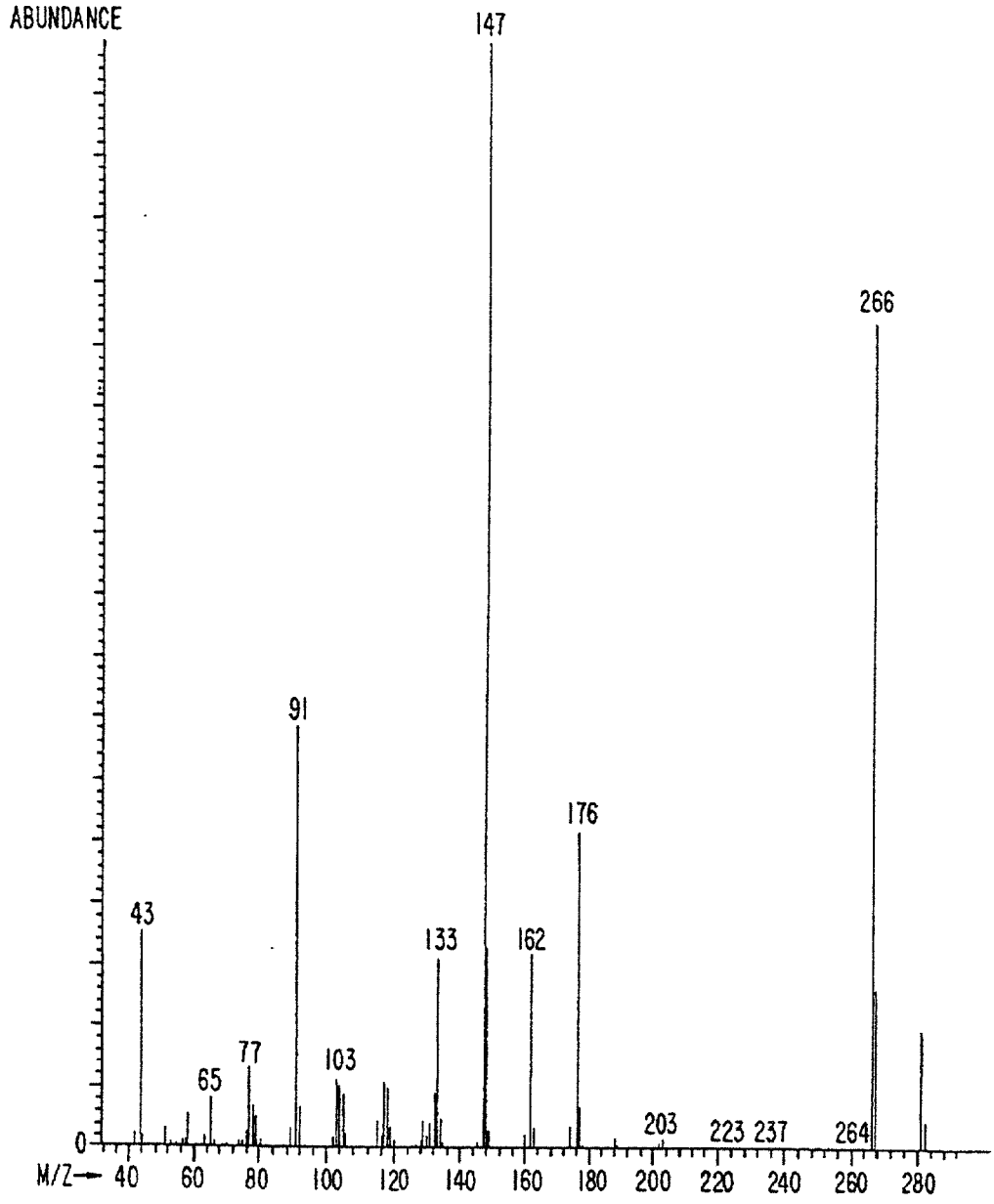
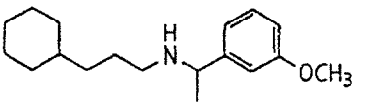

ABUNDANCE
147
266
91
176
43
133
162
77
65
103
203
223
237
264
0
M/Z→ 40 60 80 100 120 140 160 180 200 220 240 260 280

FIG. 23.


H
N
OCH3

7X

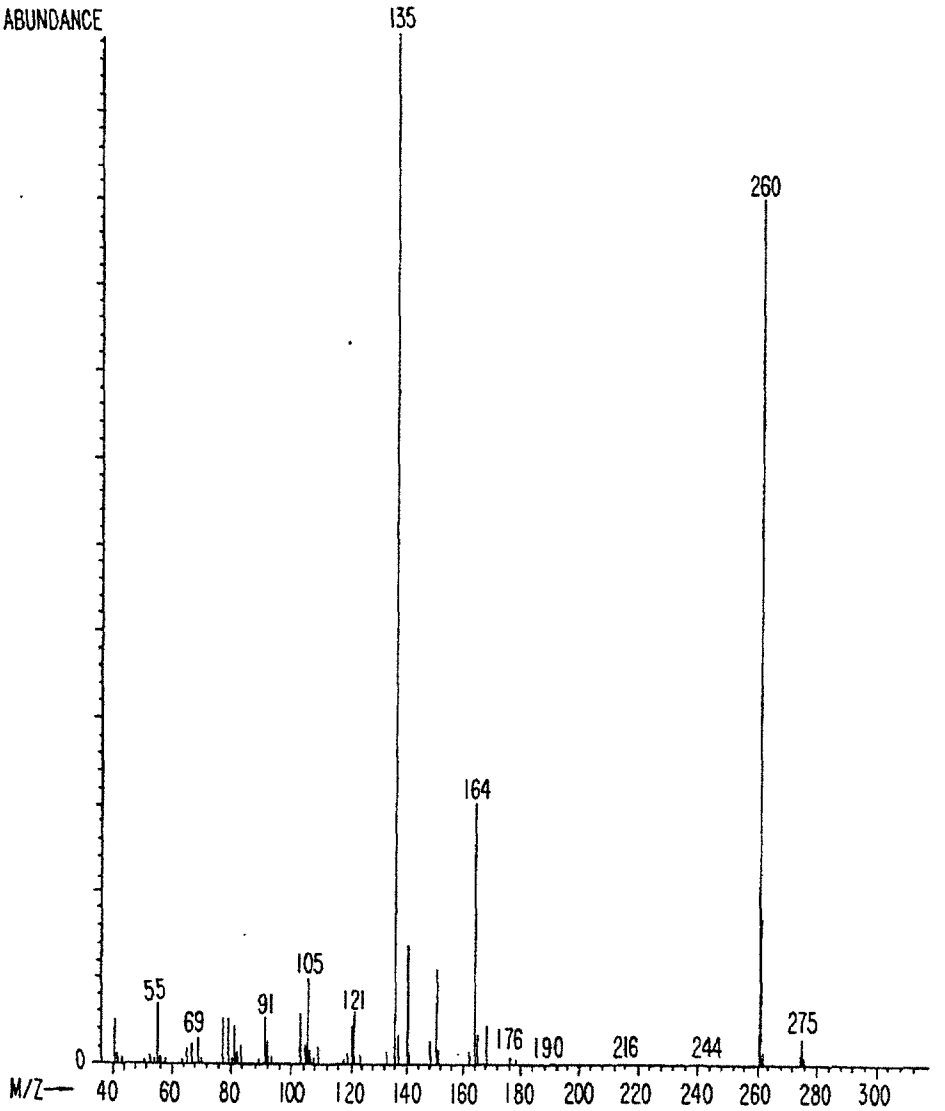

ABUNDANCE
135
260
164
105
55
69
91
121
176
190
216
244
275
0
M/Z—
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 24.

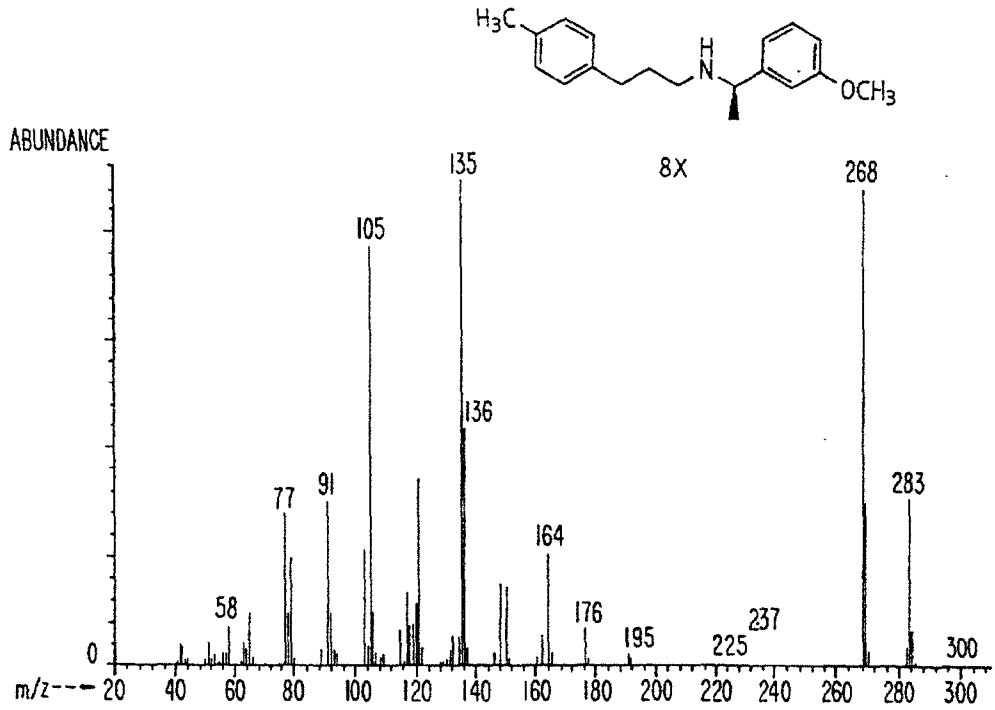

H3C
H
N
OCH3
8X
ABUNDANCE
135
268
105
136
283
77
91
164
58
176
195
225
237
300
0
m/z---→ 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300

FIG. 25.

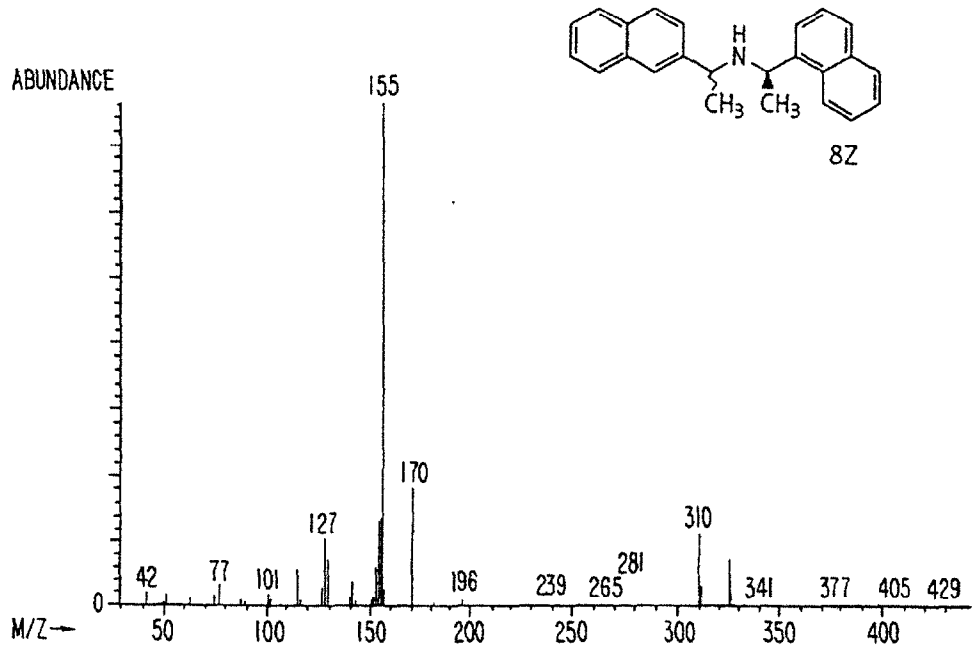

H
N
CH3 CH3
8Z
ABUNDANCE
155
170
310
127
42
77
101
196
239
265
281
341
377
405
429
0
M/Z→ 50 100 150 200 250 300 350 400

FIG. 26.

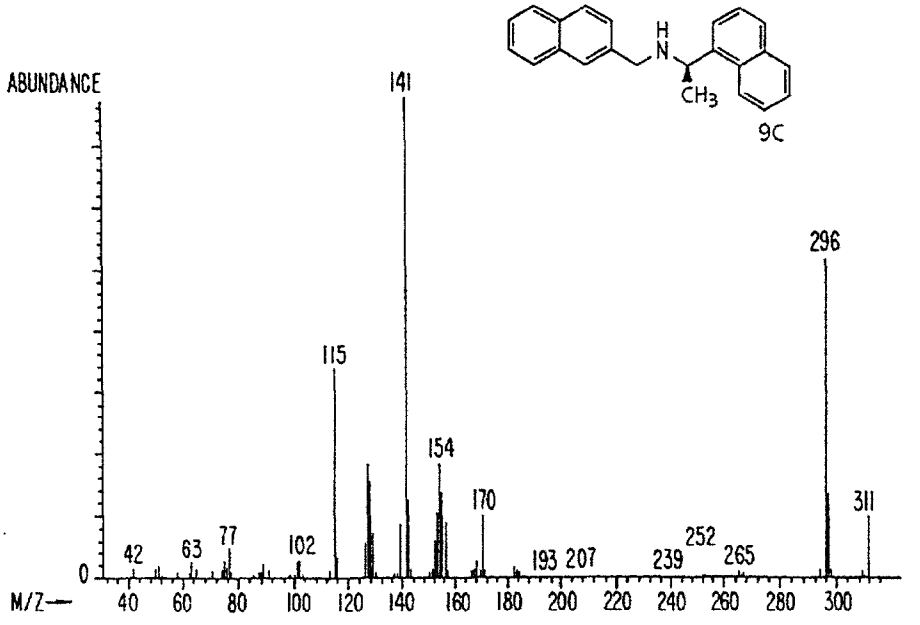

ABUNDANCE
141
296
115
154
170
311
42
63
77
102
193
207
239
252
265
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
H
N
CH3
9C

FIG. 27.

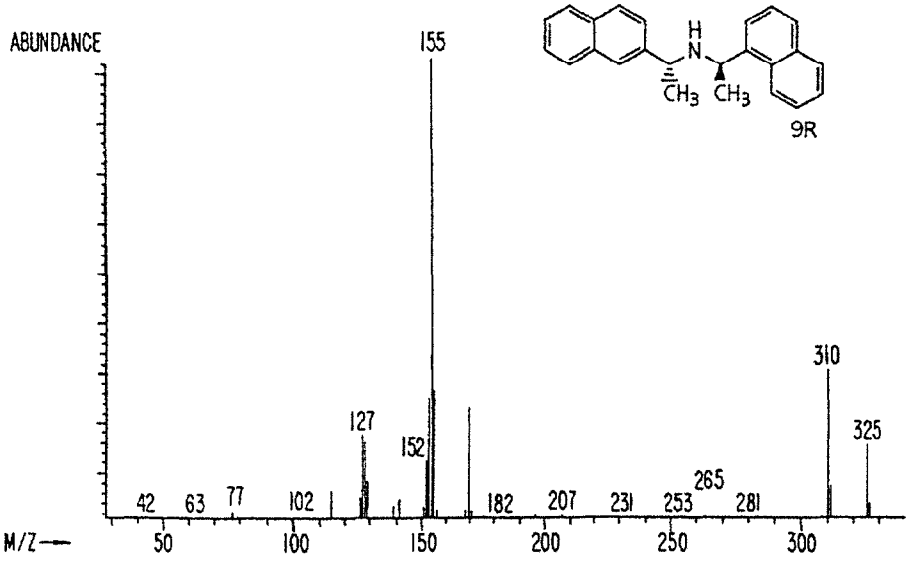

ABUNDANCE
155
310
325
127
152
42
63
77
102
182
207
231
253
265
281
M/Z
50
100
150
200
250
300
H
N
CH3
CH3
9R

FIG. 28.

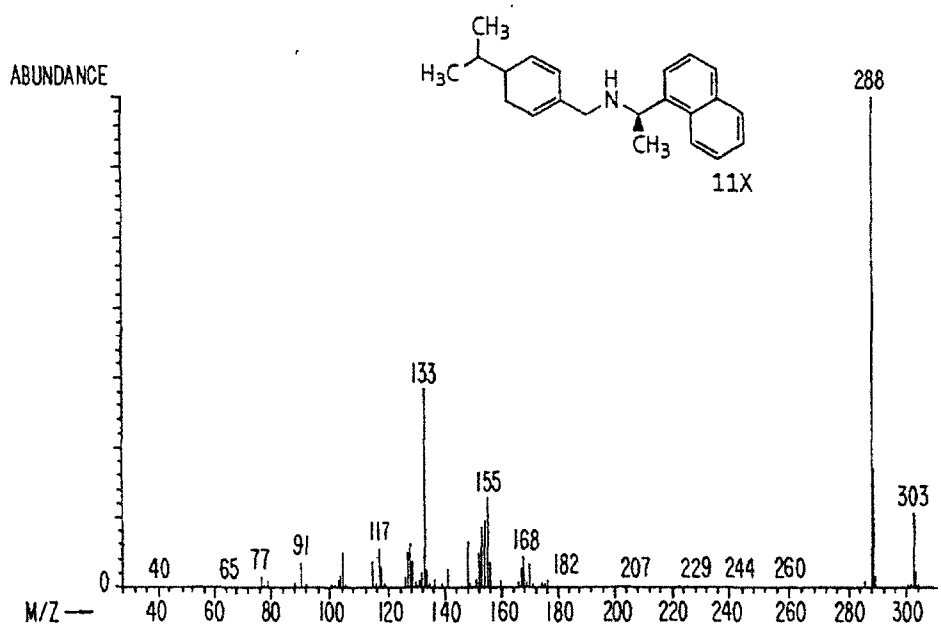

ABUNDANCE
CH3
H3C
H
N
CH3
11X
288
133
155
303
117
168
91
77
65
40
182
207
229
244
260
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 29.

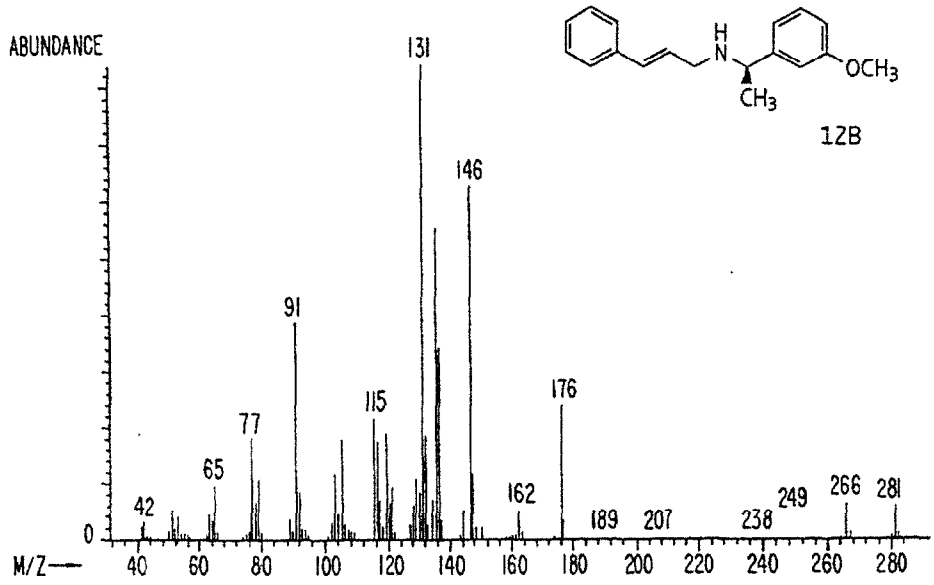

ABUNDANCE
131
H
N
OCH3
CH3
12B
146
91
176
115
77
65
42
162
189
207
238
249
266
281
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 30.

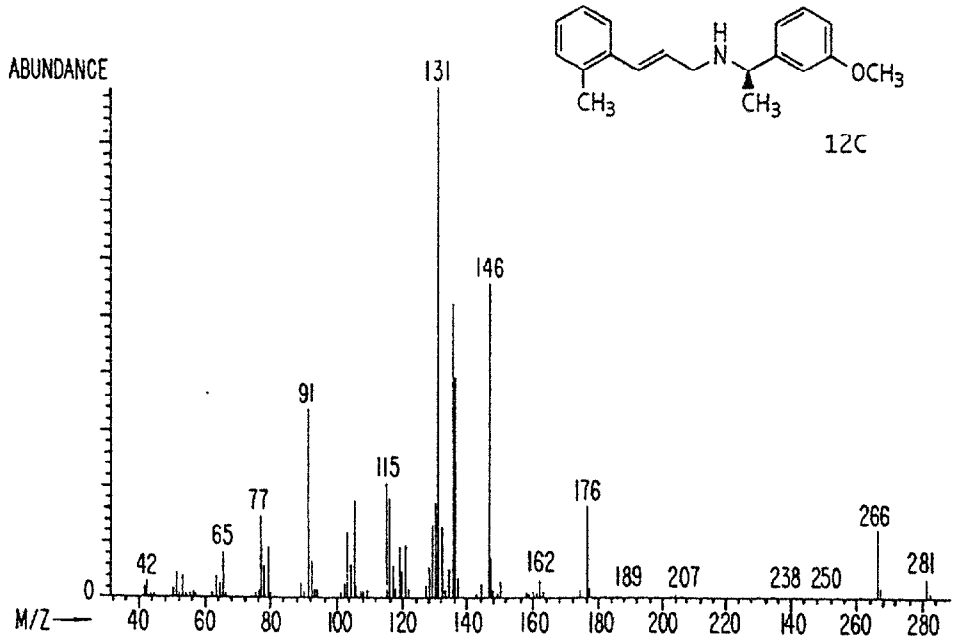

ABUNDANCE
M/Z
12C
131
146
91
115
77
65
42
176
162
189
207
238
250
266
281
0
40
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 31.

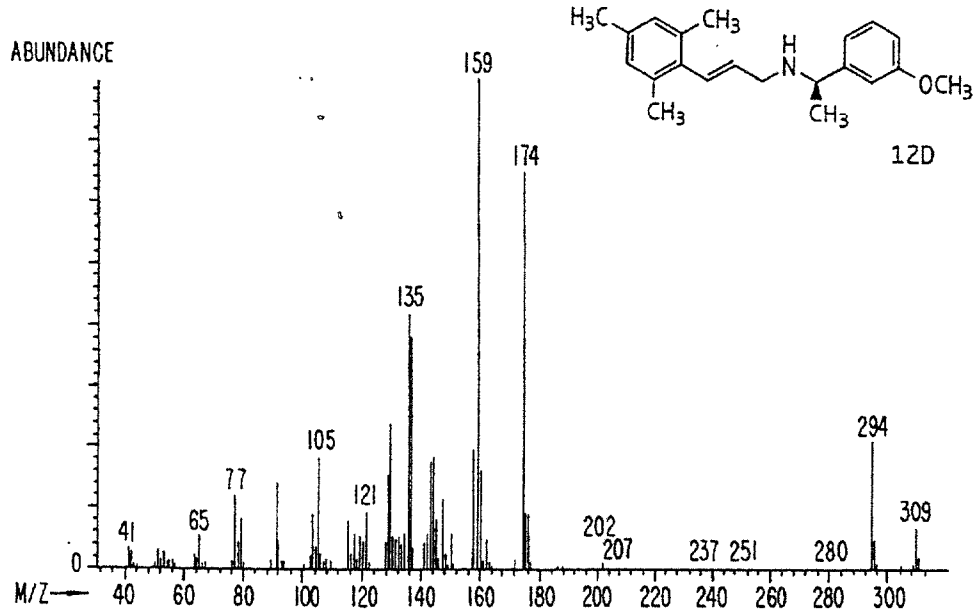

ABUNDANCE
M/Z
12D
159
174
135
105
77
121
41
65
202
207
237
251
280
294
309
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 32.

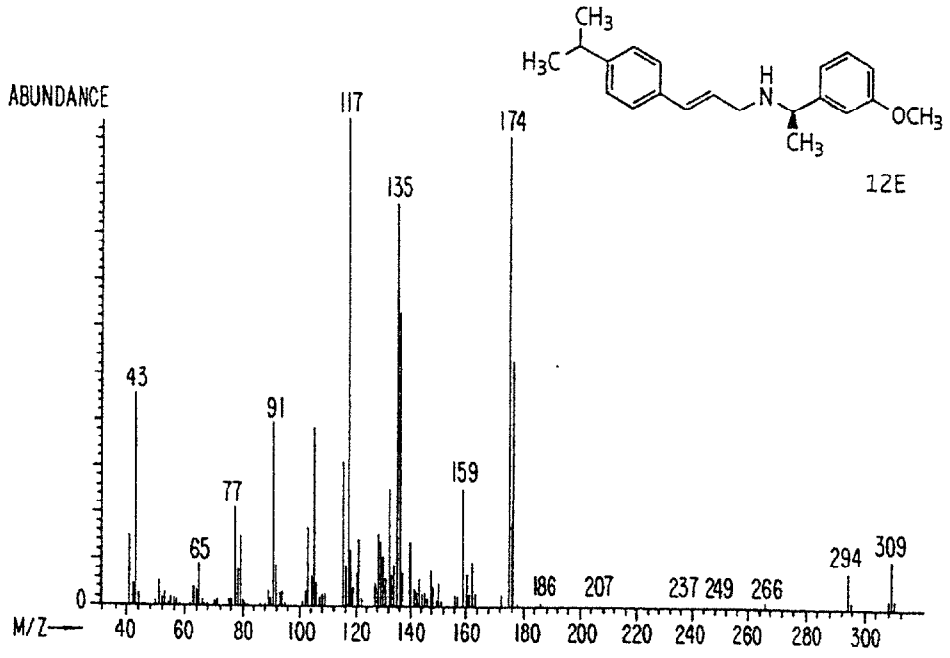

ABUNDANCE
M/Z
12E
43
65
77
91
117
135
159
174
186
207
237
249
266
294
309

FIG. 33.

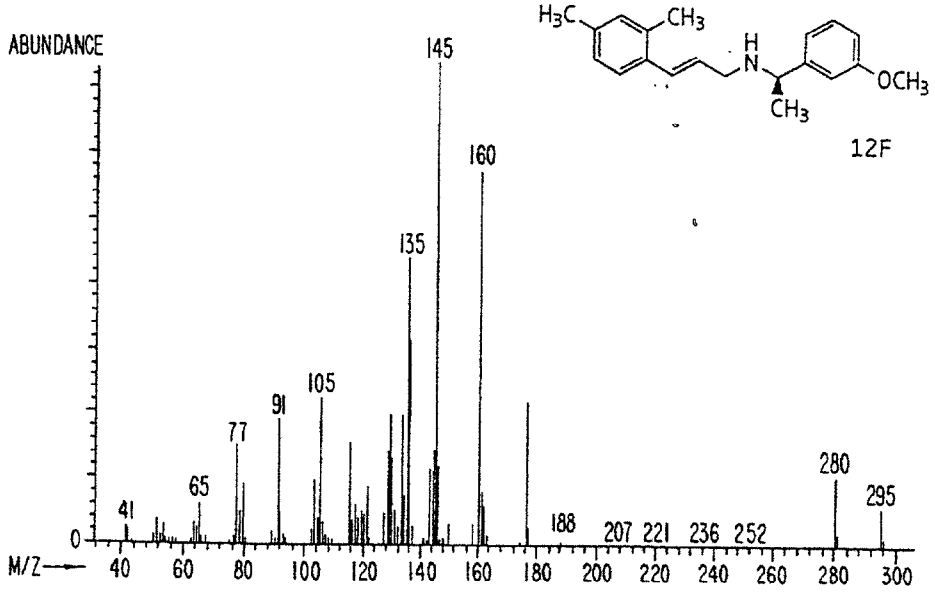

ABUNDANCE
M/Z
12F
41
65
77
91
105
135
145
160
188
207
221
236
252
280
295

FIG. 34.

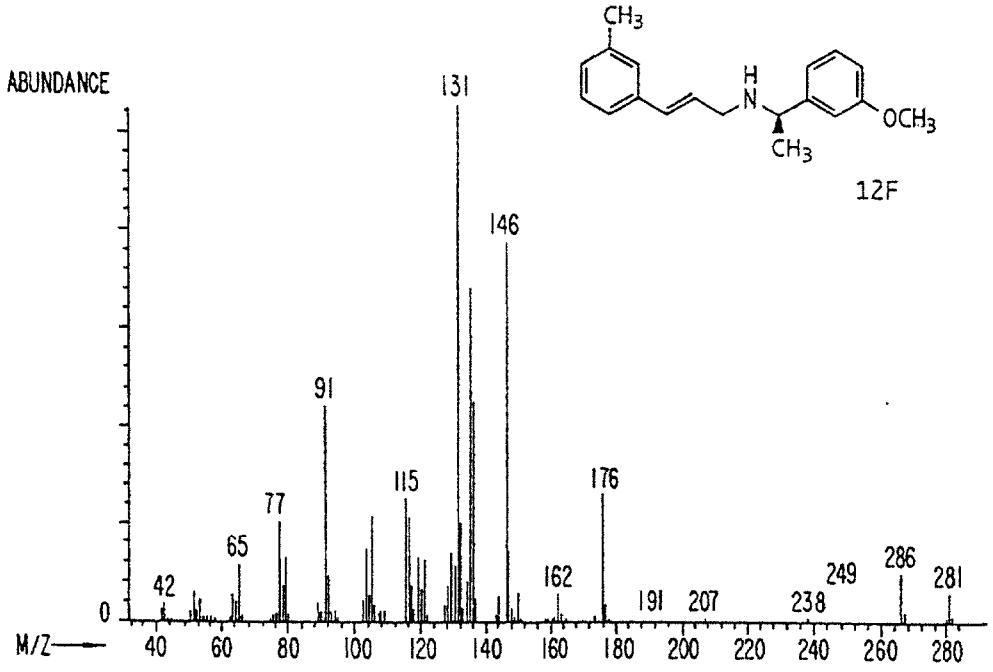

ABUNDANCE
M/Z
0
40 60 80 100 120 140 160 180 200 220 240 260 280
42 65 77 91 115 131 146 162 176 191 207 238 249 286 281
CH3
H
N
OCH3
CH3
12F

FIG. 35.

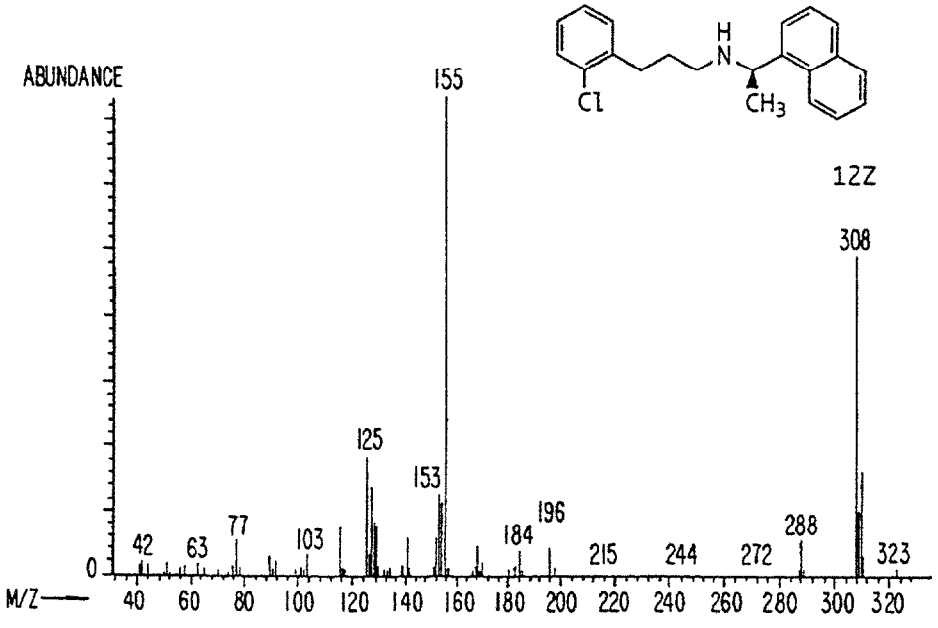

ABUNDANCE
M/Z
0
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320
42 63 77 103 125 153 155 184 196 215 244 272 288 308 323
H
N
Cl
CH3
12Z

FIG. 36.

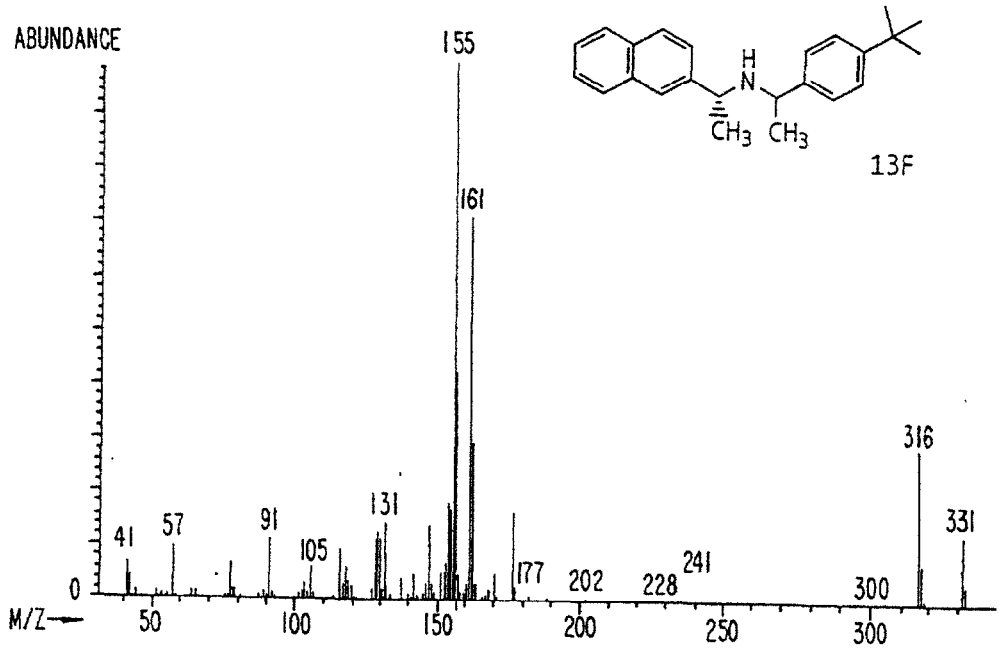

ABUNDANCE
155
161
316
331
41
57
91
105
131
177
202
228
241
300
0
M/Z
50
100
150
200
250
300
H
N
CH3
CH3
13F

FIG. 37.

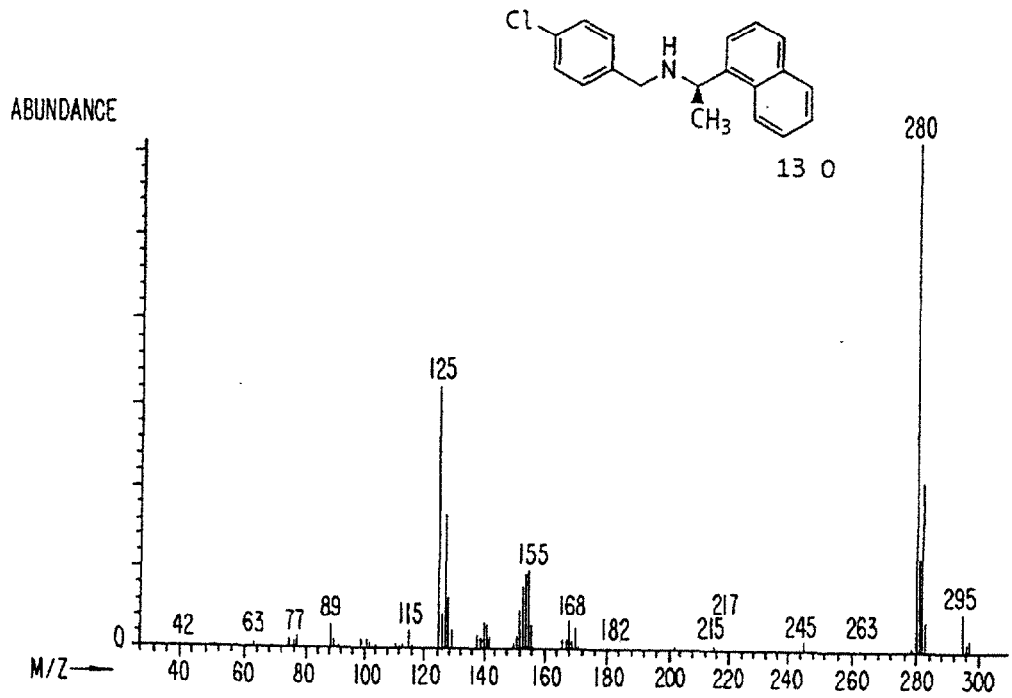

ABUNDANCE
Cl
H
N
CH3
13 O
280
125
155
42
63
77
89
115
168
182
217
215
245
263
295
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 38.

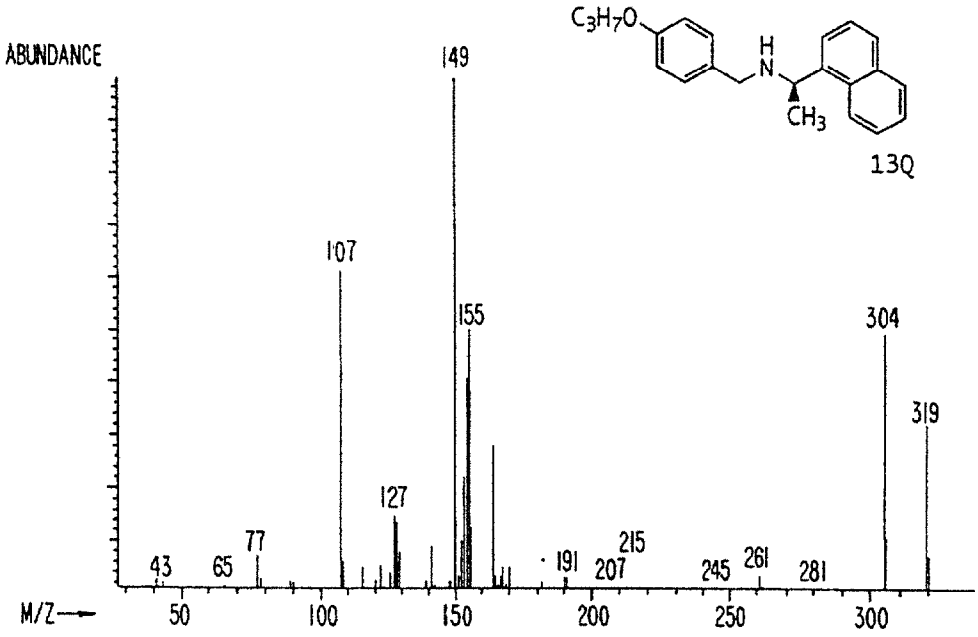

ABUNDANCE
149
107
155
304
319
127
77
43
65
191
207
215
245
261
281
M/Z
50
100
150
200
250
300
C_3H_7O
H
N
CH_3
13Q

FIG. 39.

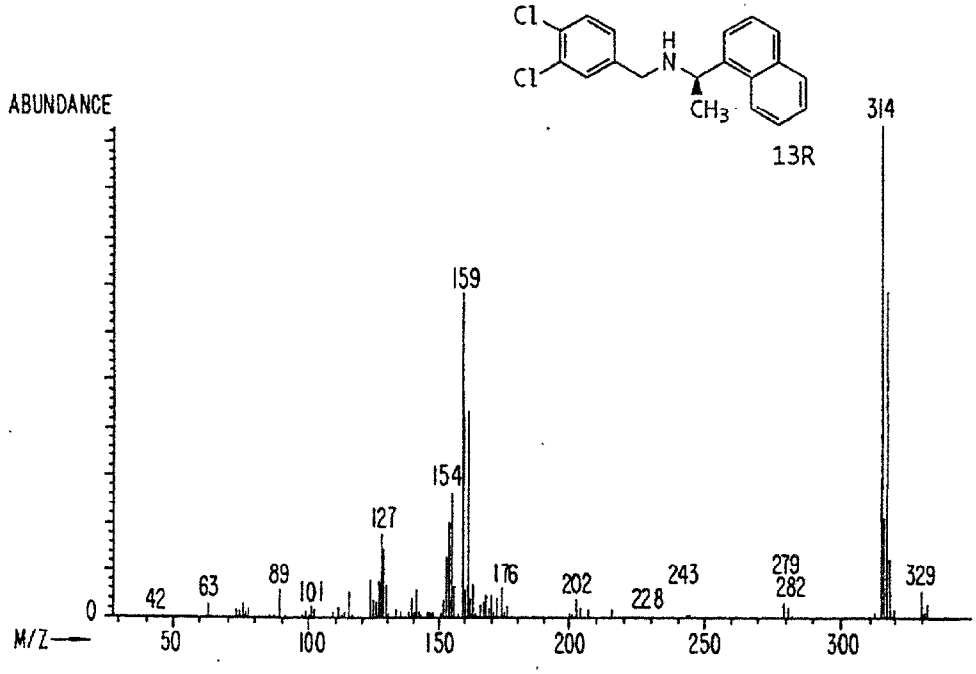

ABUNDANCE
Cl
Cl
H
N
CH_3
13R
314
159
154
127
42
63
89
101
176
202
228
243
279
282
329
0
M/Z
50
100
150
200
250
300

FIG. 40.

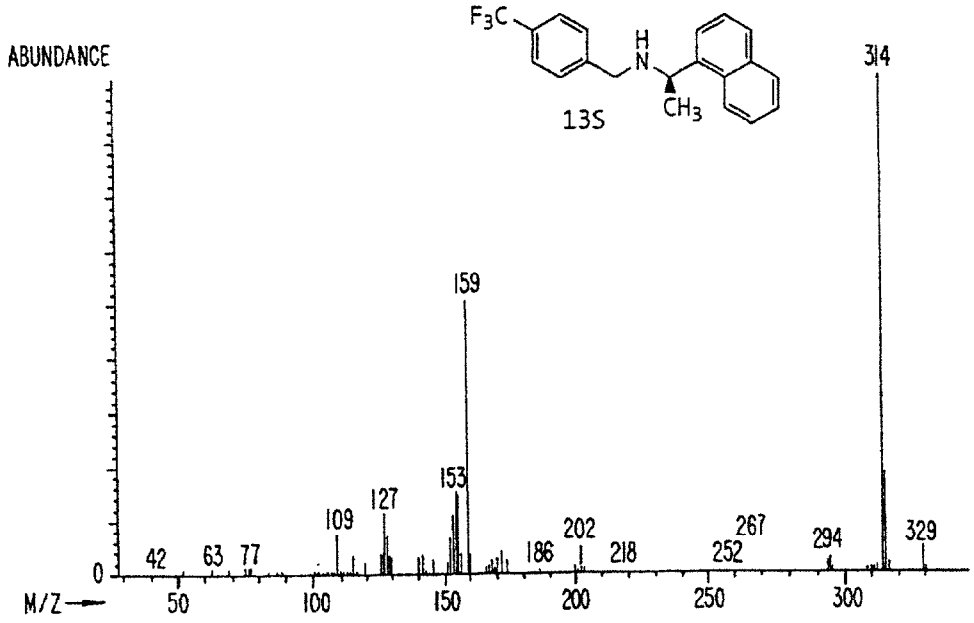

ABUNDANCE
F3C
H
N
CH3
13S
314
159
153
127
109
42
63
77
186
202
218
252
267
294
329
0
M/Z
50
100
150
200
250
300

FIG. 41.

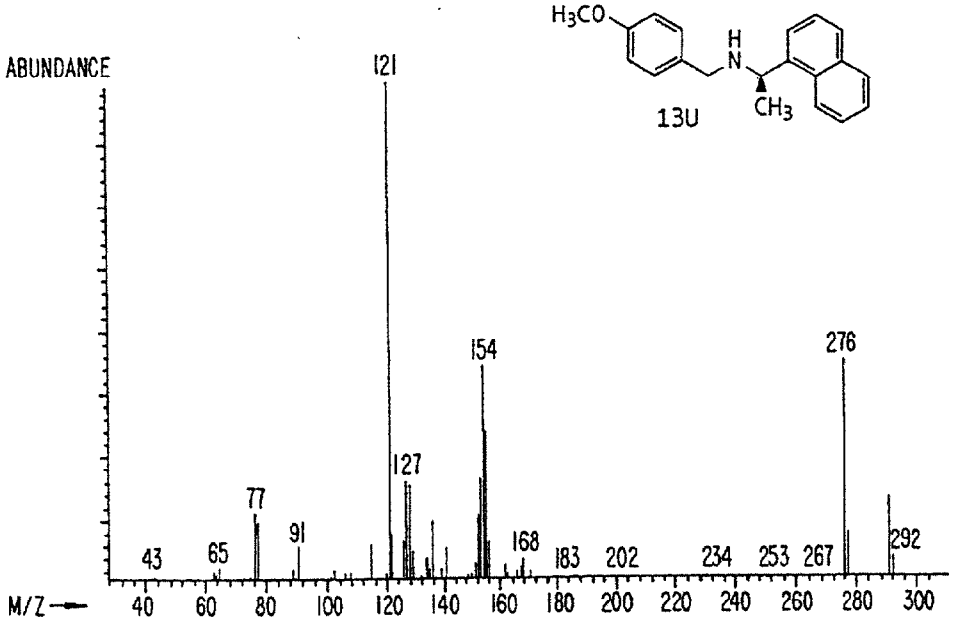

ABUNDANCE
H3CO
H
N
CH3
13U
121
154
276
127
77
91
43
65
168
183
202
234
253
267
292
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 42.

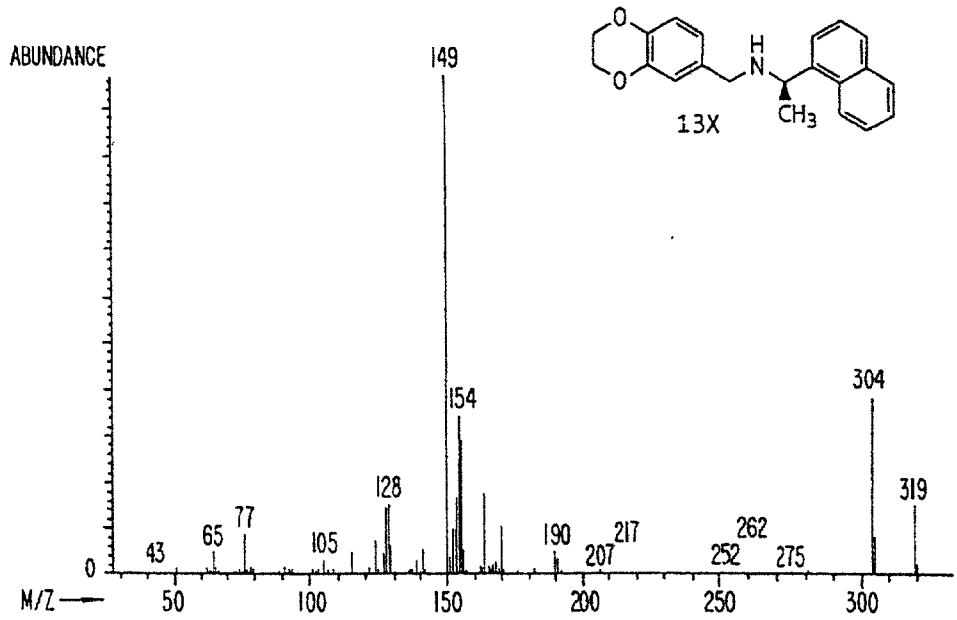

ABUNDANCE
149
154
128
43
65
77
105
190
207
217
252
262
275
304
319
0
M/Z
50
100
150
200
250
300
13X
H
N
CH3
O
O

FIG. 43.

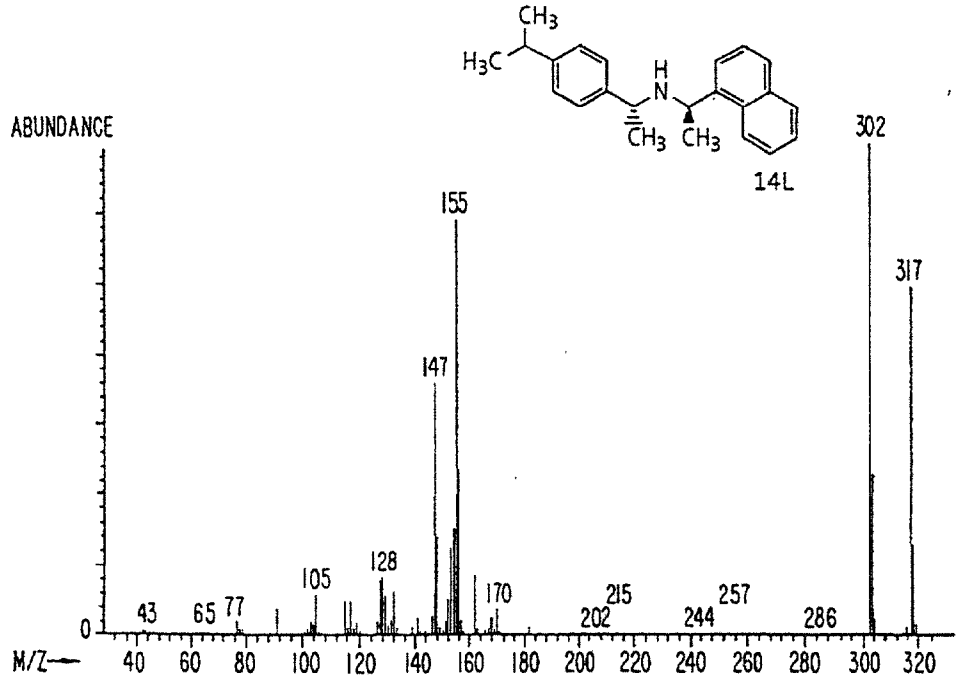

ABUNDANCE
155
147
128
105
43
65
77
170
202
215
244
257
286
302
317
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
14L
CH3
H3C
H
N
CH3
CH3

FIG. 44.

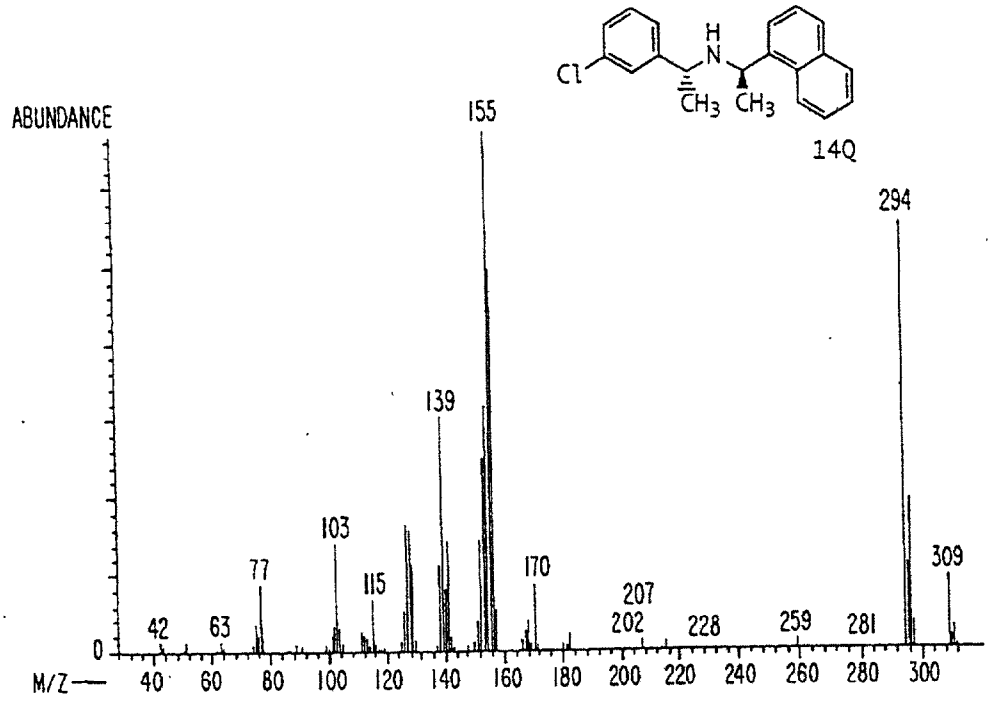

ABUNDANCE
155
294
139
103
77
115
170
207
202
228
259
281
309
42
63
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
Cl
H
N
CH3
CH3
14Q

FIG. 45.

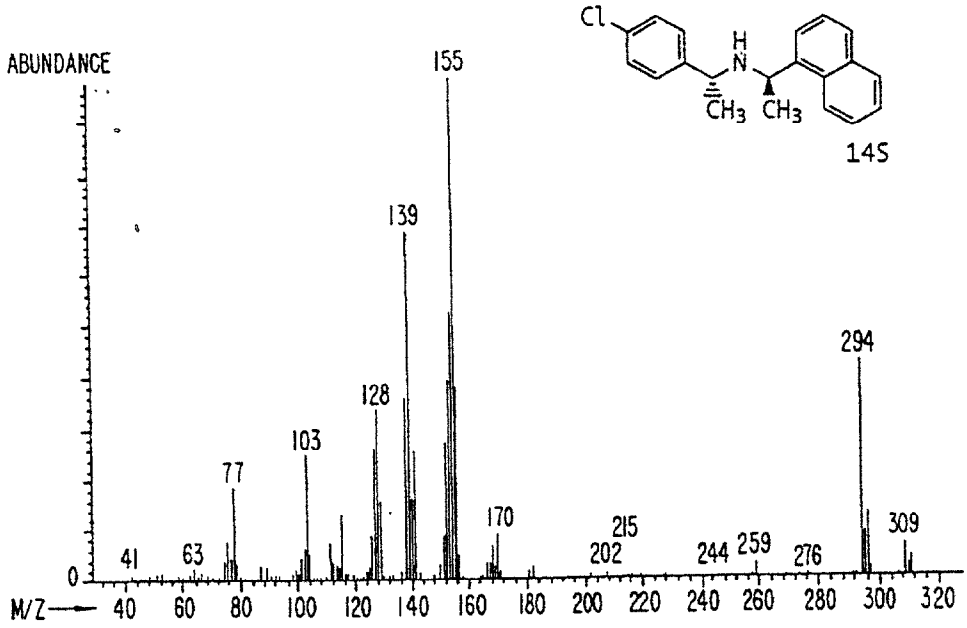

ABUNDANCE
155
139
294
128
103
77
170
215
202
244
259
276
309
41
63
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
Cl
H
N
CH3
CH3
14S

FIG. 46.

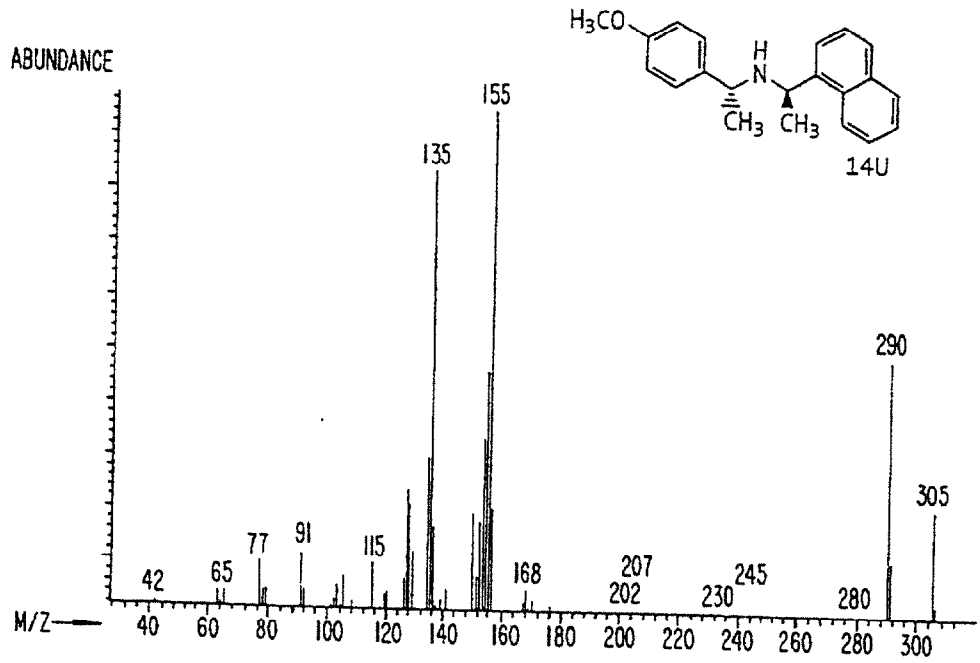

ABUNDANCE
M/Z
H3CO
H
N
CH3
CH3
14U
155
135
290
305
77
91
115
42
65
168
207
202
230
245
280
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 47.

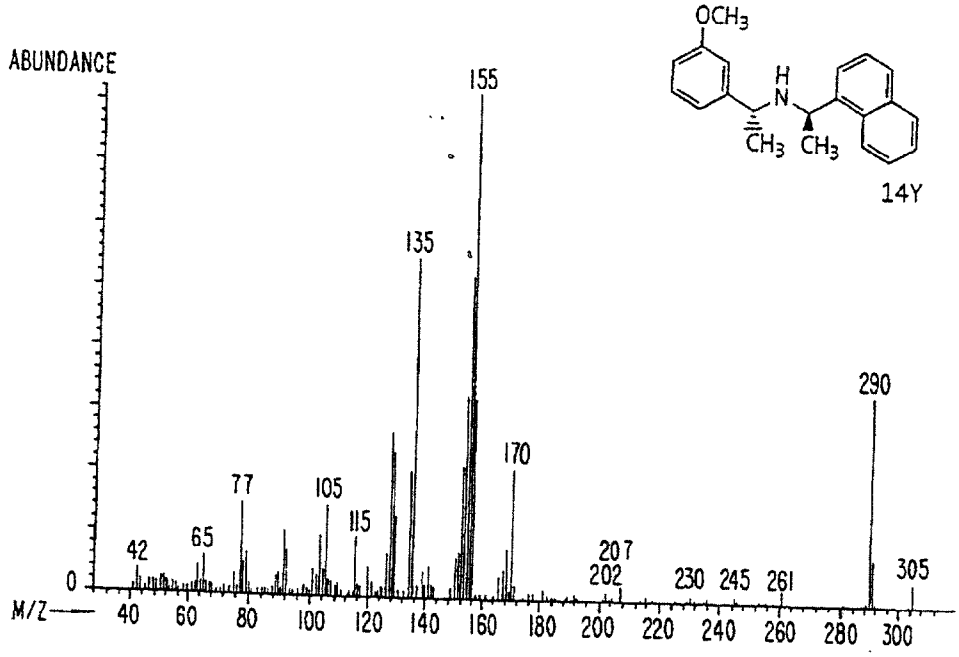

ABUNDANCE
M/Z
OCH3
H
N
CH3
CH3
14Y
155
135
290
170
77
105
115
42
65
207
202
230
245
261
305
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 48.

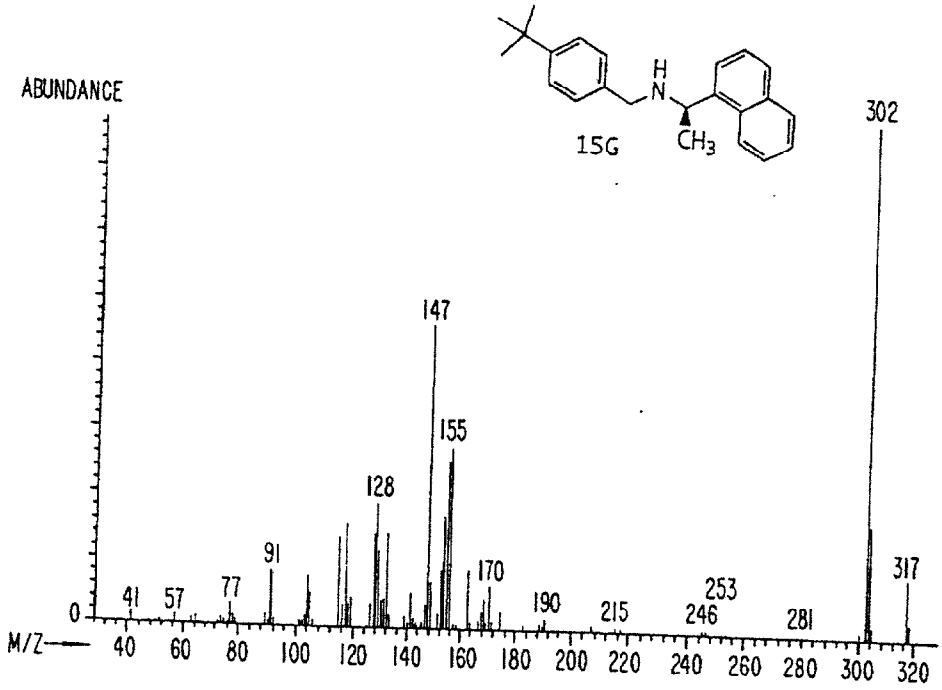

ABUNDANCE
15G
H
N
CH3
302
147
155
128
91
170
317
41
57
77
190
215
253
246
281
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320

FIG. 49.

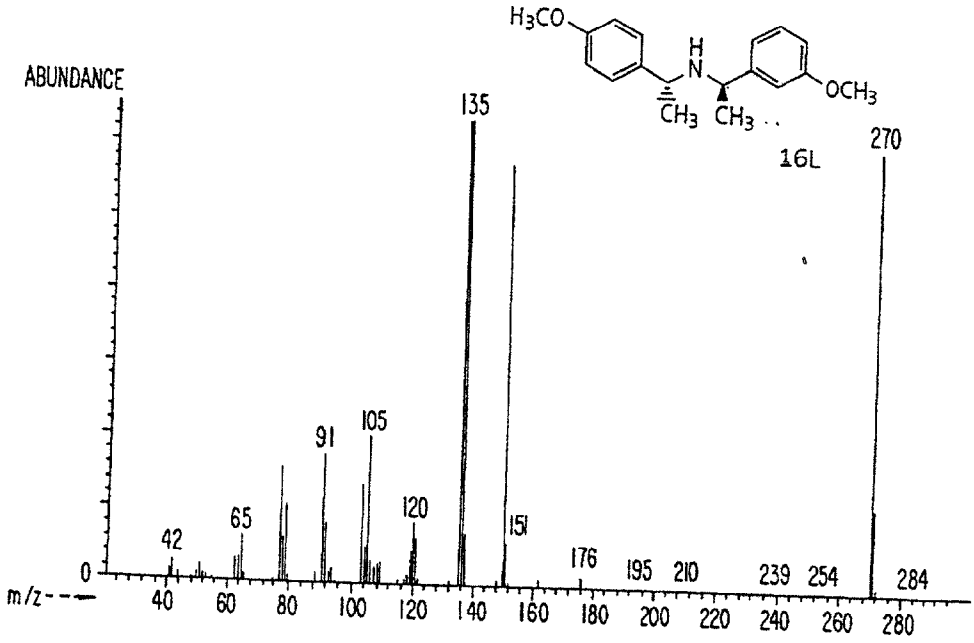

H3CO
H
N
OCH3
CH3
CH3
16L
ABUNDANCE
135
270
105
91
120
65
42
151
176
195
210
239
254
284
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 50.

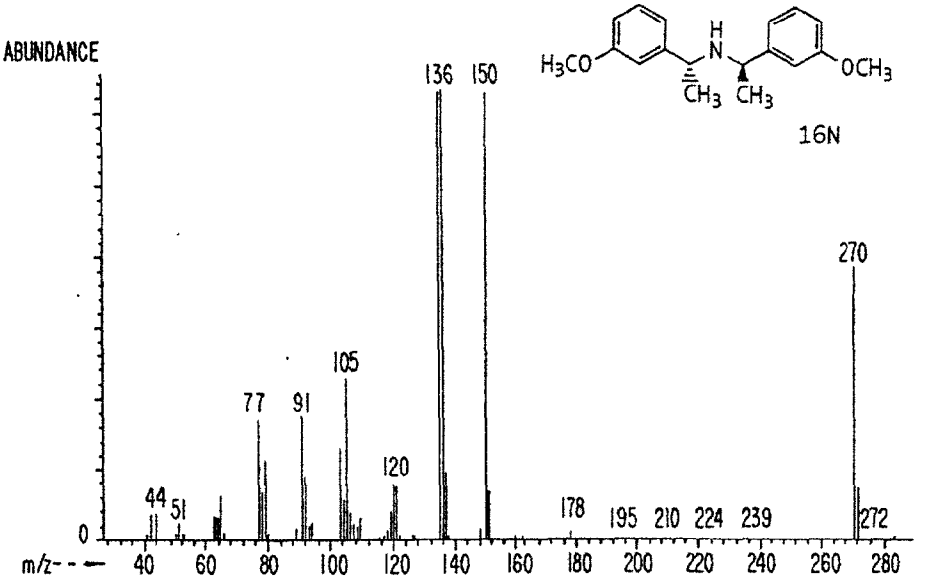

ABUNDANCE
136
150
270
105
77
91
120
44
51
178
195
210
224
239
272
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
H3CO
OCH3
H
N
CH3
CH3
16N

FIG. 51.

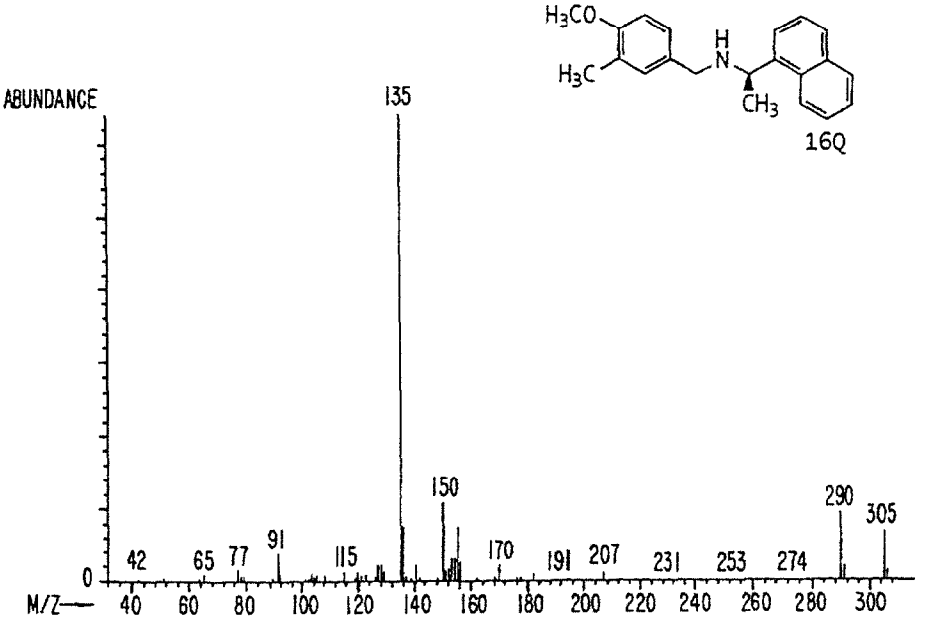

ABUNDANCE
135
150
290
305
42
65
77
91
115
170
191
207
231
253
274
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
H3CO
H3C
H
N
CH3
16Q

FIG. 52.

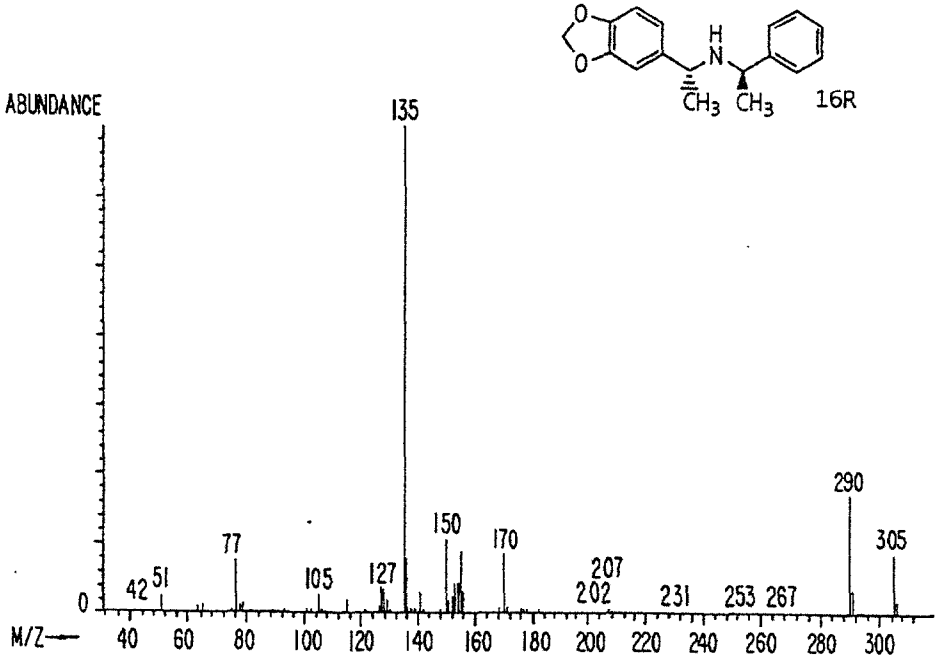

ABUNDANCE
135
290
305
150
170
77
207
202
42
51
105
127
231
253
267
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
16R

FIG. 53.

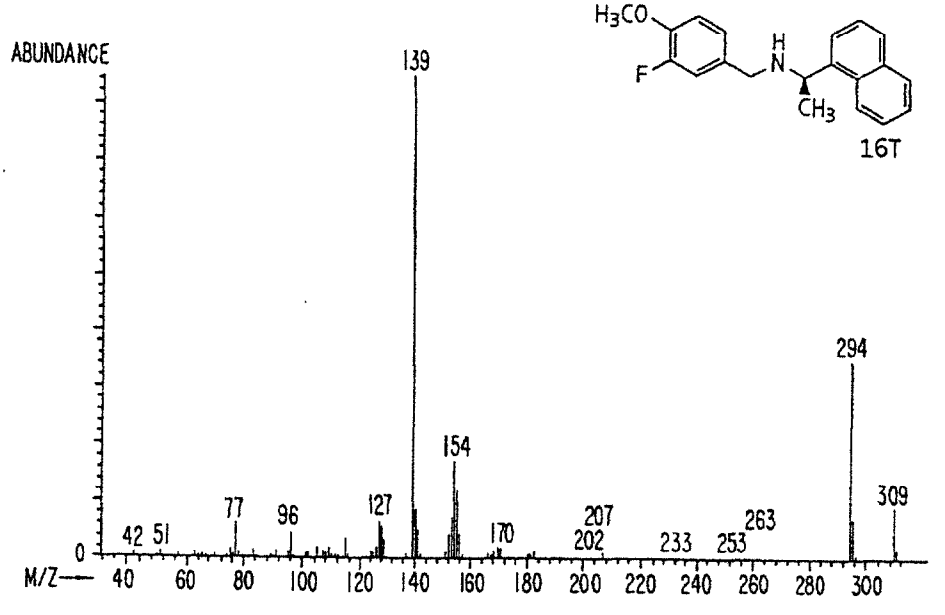

ABUNDANCE
139
294
154
309
77
96
127
207
202
263
42
51
170
233
253
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
16T

FIG. 54.

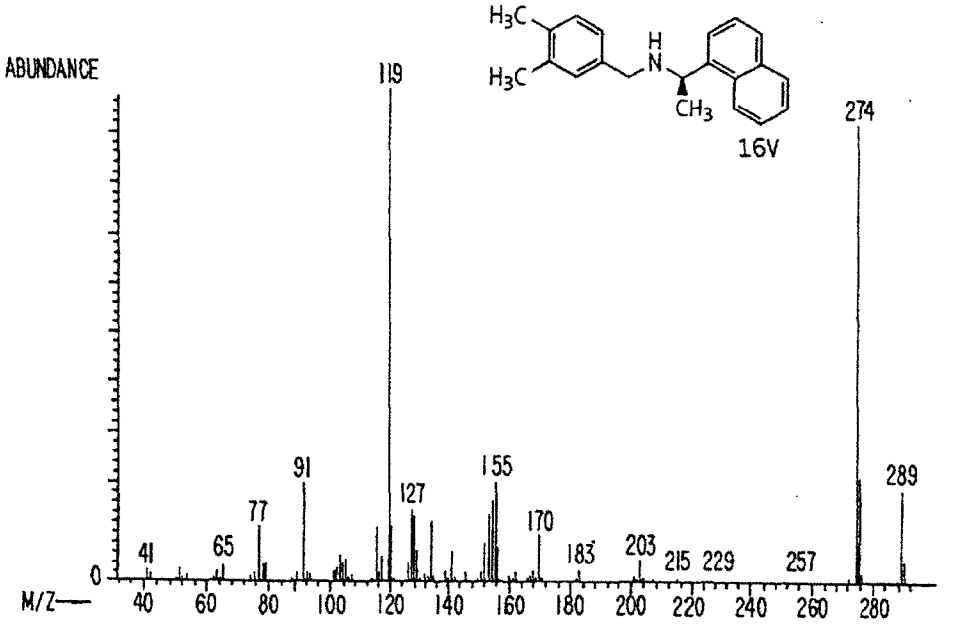

ABUNDANCE
M/Z
16V
119
274
91
155
289
127
77
170
41
65
183
203
215
229
257

FIG. 55.

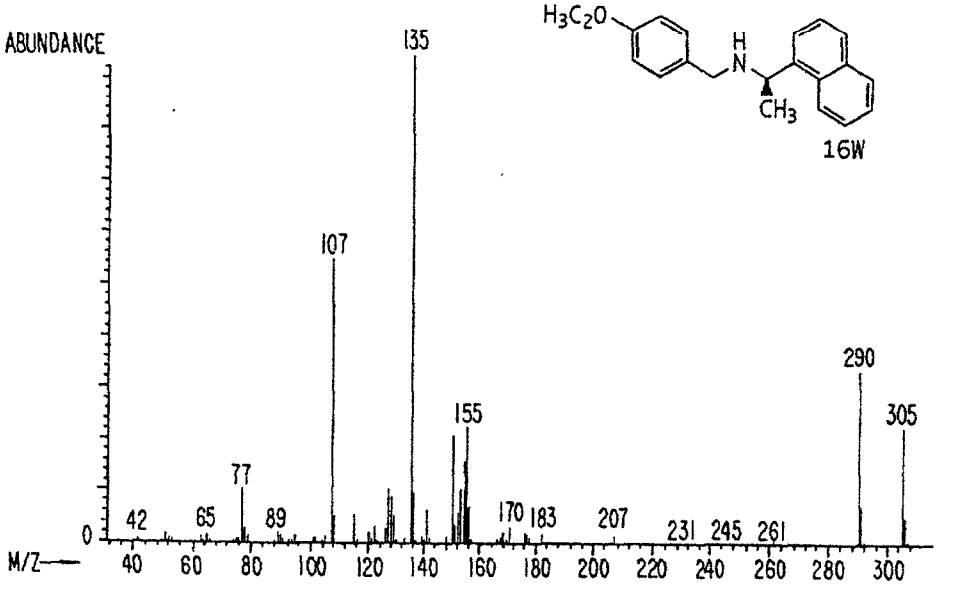

ABUNDANCE
M/Z
16W
135
107
290
155
305
77
42
65
89
170
183
207
231
245
261

FIG. 56.

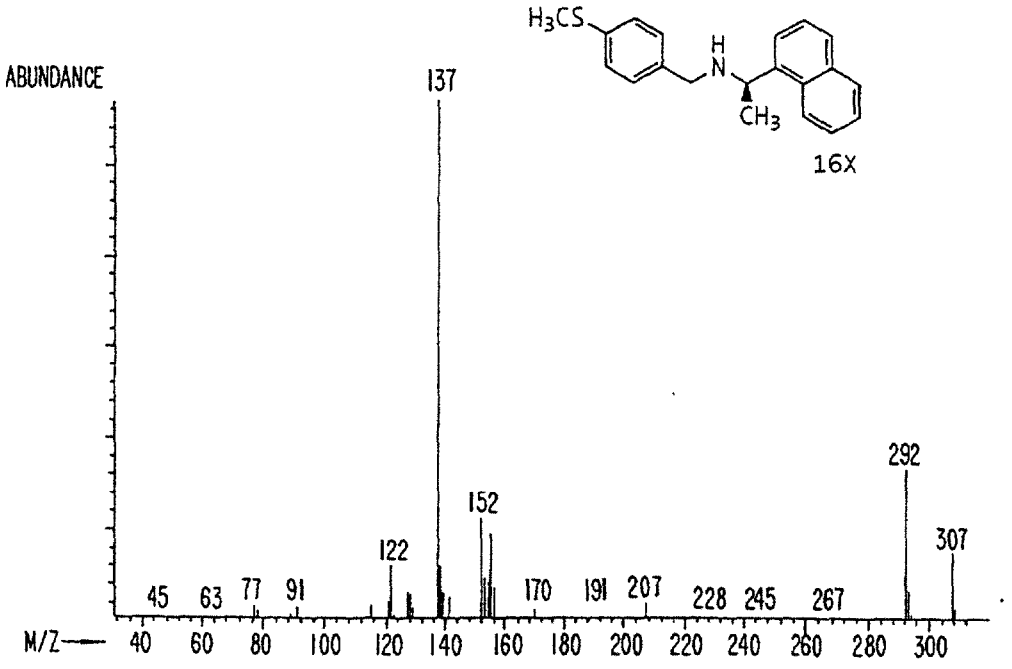

ABUNDANCE
137
292
152
307
122
45 63 77 91
170 191 207 228 245 267
M/Z
40 60 80 100 120 140 160 180 200 220 240 260 280 300
H3CS
H
N
CH3
16X

FIG. 57

ABUNDANCE
217
372
155
90
232
127
152
387
51 77
191
260 281 310 331
0
M/Z
50 100 150 200 250 300 350
I
H
N
CH3
17E

FIG. 58.

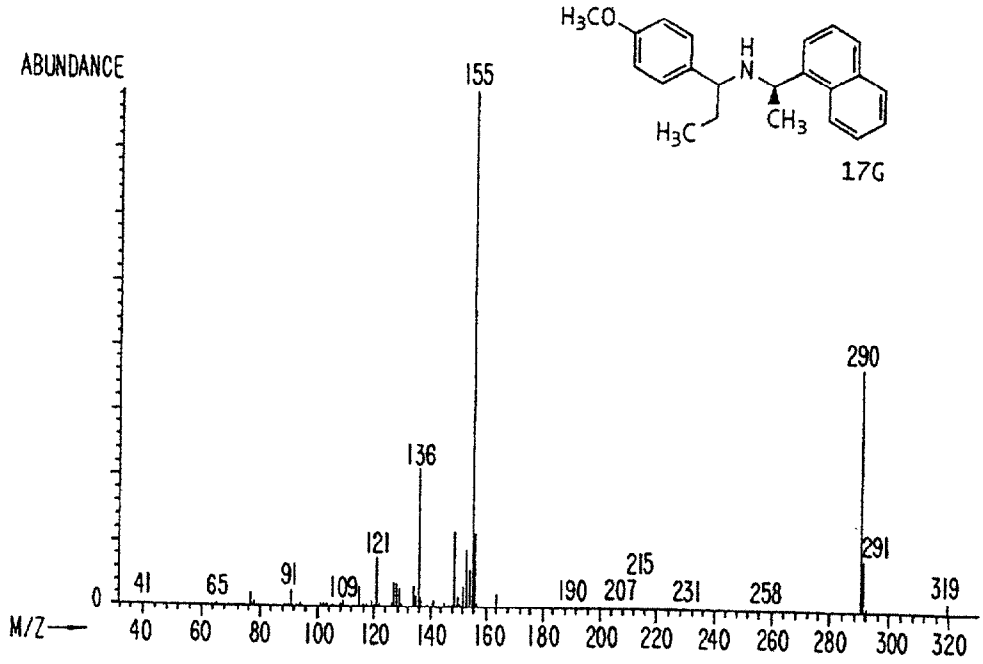

ABUNDANCE
155
290
136
121
291
215
41
65
91
109
190
207
231
258
319
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
H3CO
H
N
CH3
H3C
17G

FIG. 59.

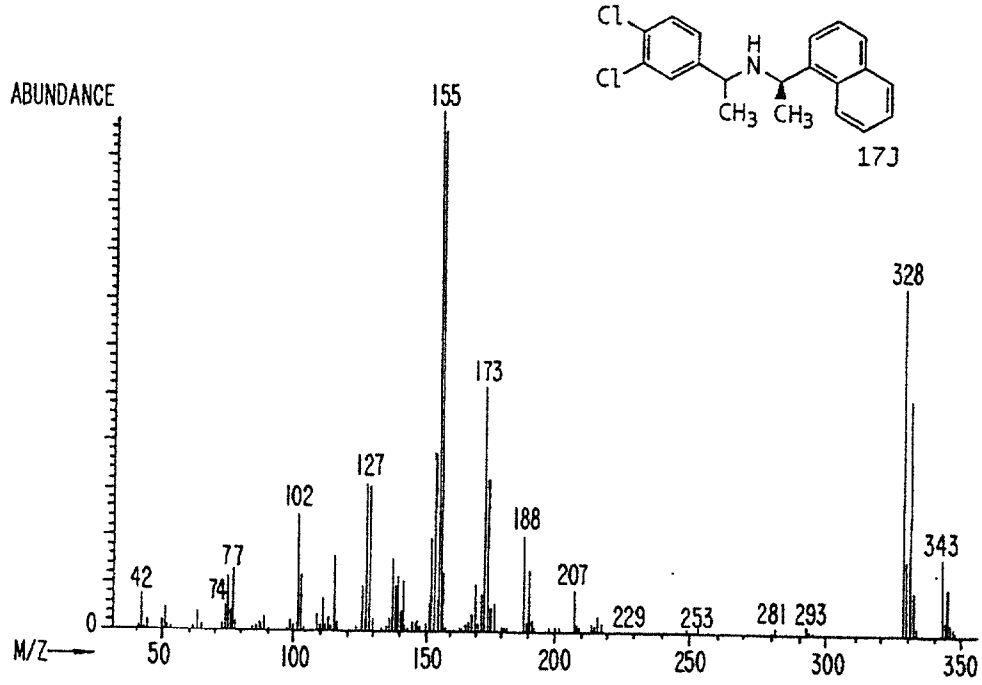

ABUNDANCE
155
328
173
127
102
188
343
77
42
74
207
229
253
281
293
0
M/Z
50
100
150
200
250
300
350
Cl
Cl
H
N
CH3
CH3
17J

FIG. 60.

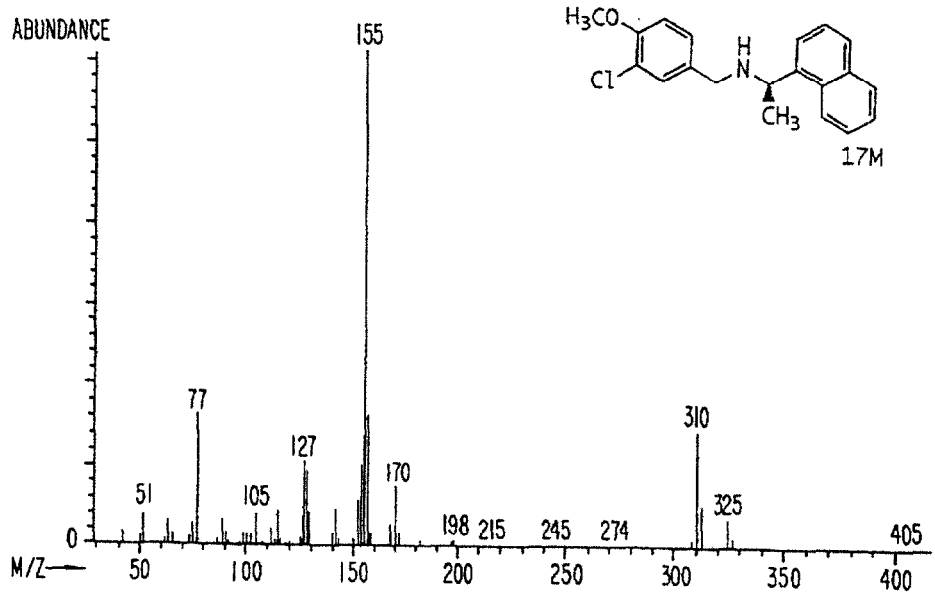

ABUNDANCE
155
H3CO
Cl
H
N
CH3
17M
77
310
127
170
51
105
325
198
215
245
274
405
0
M/Z
50
100
150
200
250
300
350
400

FIG. 61.

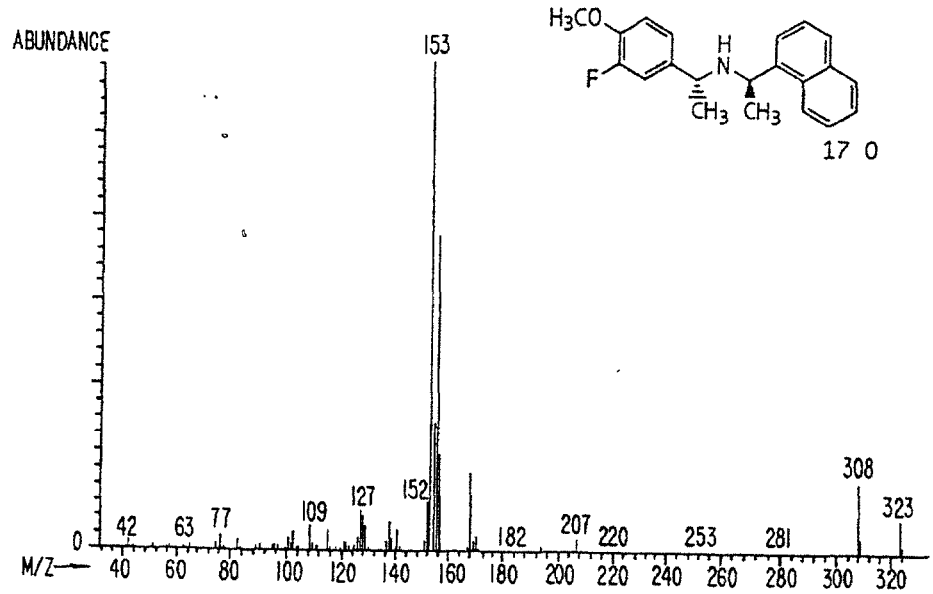

ABUNDANCE
153
H3CO
F
H
N
CH3
CH3
17 0
308
323
152
127
42
63
77
109
182
207
220
253
281
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320

FIG. 62.

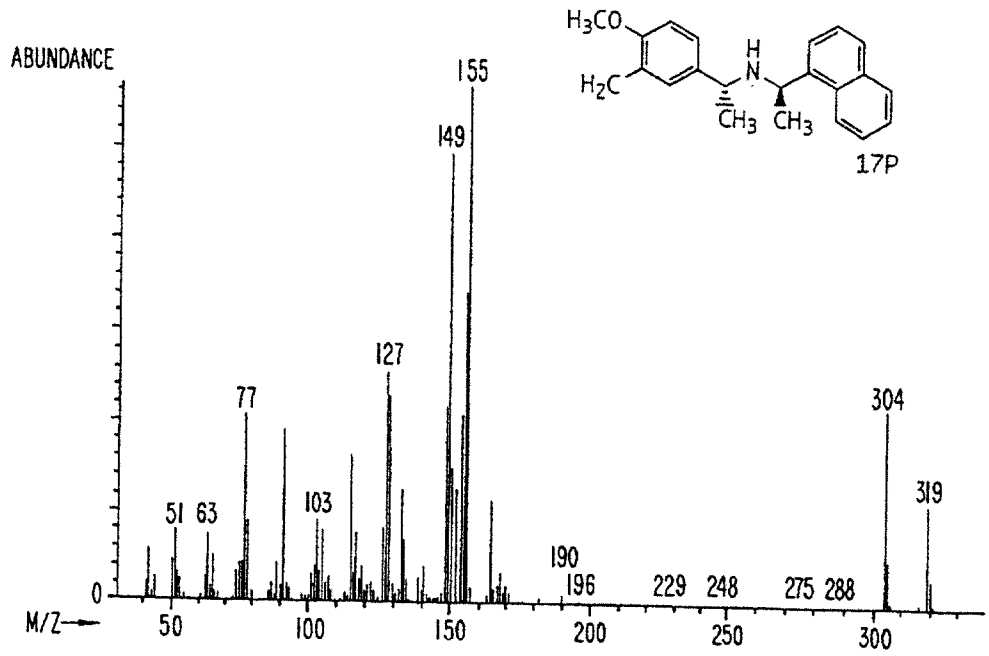

ABUNDANCE
155
149
127
77
304
319
51 63
103
190
196
229 248
275 288
0
M/Z
50
100
150
200
250
300
H3CO
H2C
H
N
CH3 CH3
17P

FIG. 63.

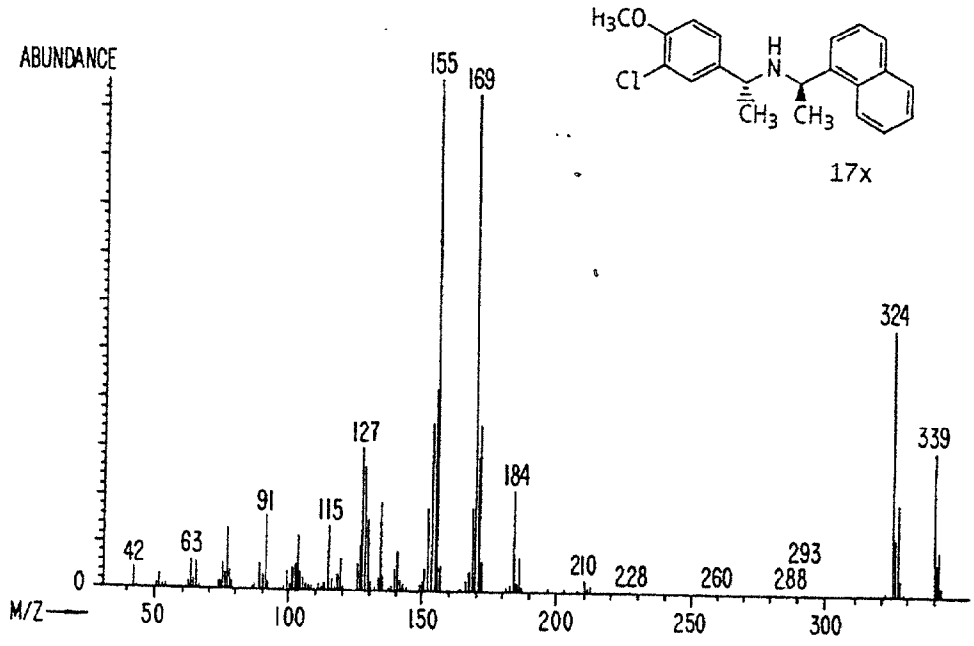

ABUNDANCE
155
169
324
339
127
184
91
115
42
63
210
228
260
293
288
0
M/Z
50
100
150
200
250
300
H3CO
Cl
H
N
CH3 CH3
17x

FIG. 64

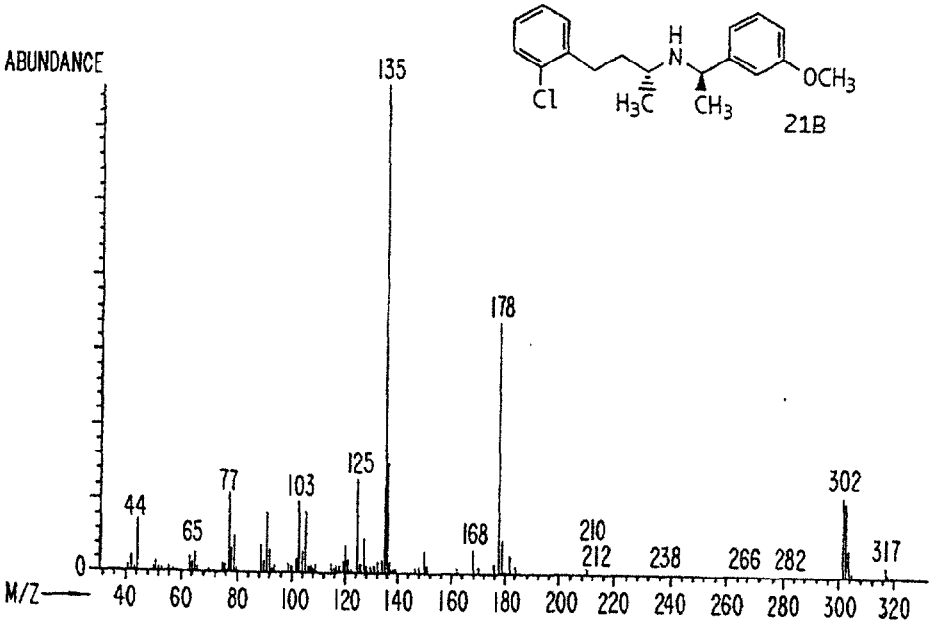

ABUNDANCE
135
178
125
77
103
44
65
168
210
212
238
266
282
302
317
0
M/Z
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320
H
N
Cl
H3C
CH3
OCH3
21B

FIG. 65.

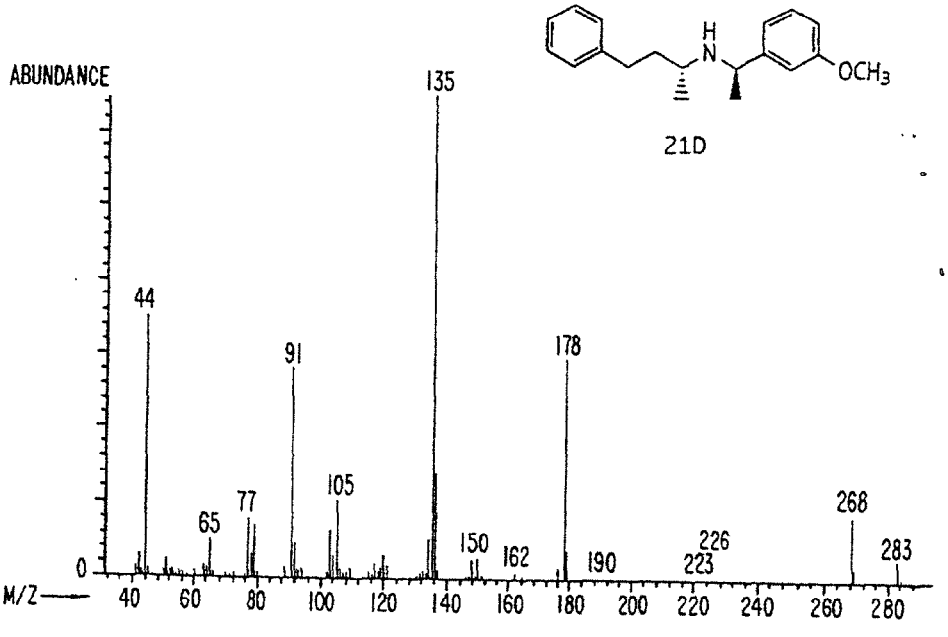

ABUNDANCE
135
44
91
178
105
77
65
150
162
190
226
223
268
283
0
M/Z
40 60 80 100 120 140 160 180 200 220 240 260 280
H
N
OCH3
21D

FIG. 66.

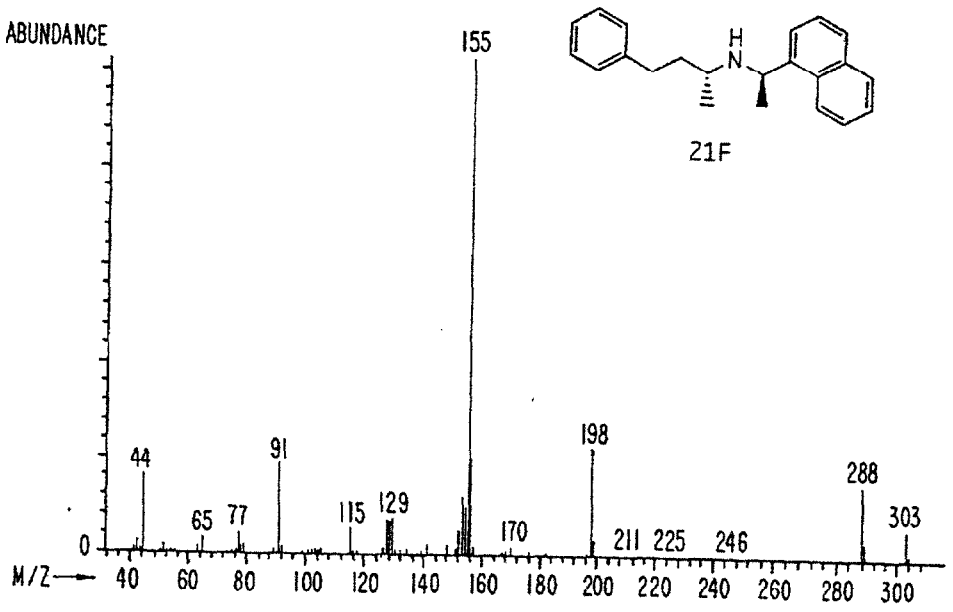

ABUNDANCE
155
H
N
21F
44
91
198
288
65
77
115
129
170
211
225
246
303
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 67.

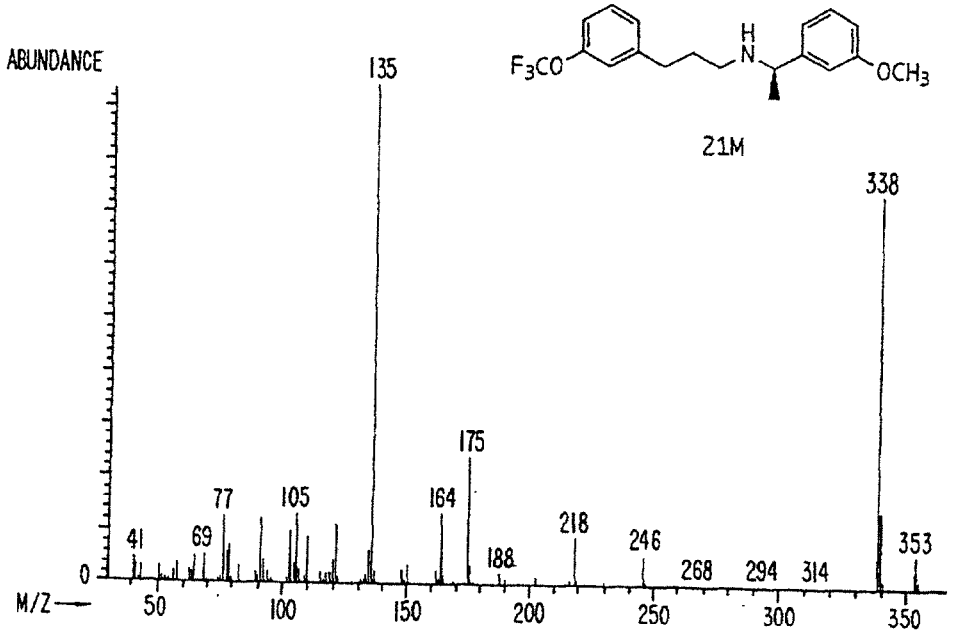

ABUNDANCE
135
F3CO
H
N
OCH3
21M
338
175
77
105
164
218
246
41
69
188
268
294
314
353
0
M/Z
50
100
150
200
250
300
350

FIG. 68.

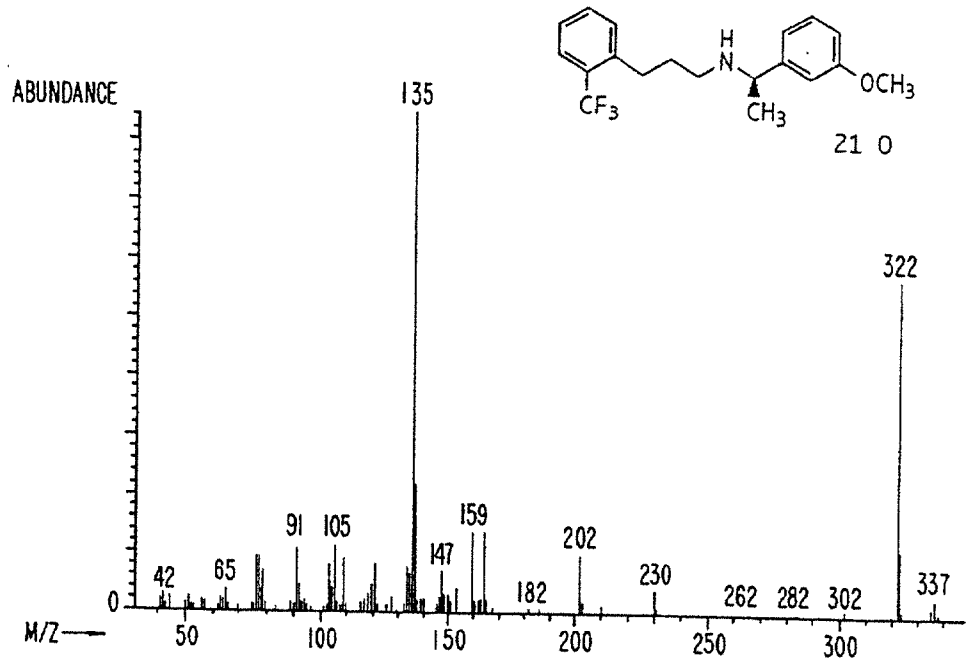

ABUNDANCE
135
322
91
105
159
147
202
42
65
182
230
262
282
302
337
0
M/Z
50
100
150
200
250
300
CF3
H
N
CH3
OCH3
21 O

FIG. 69.

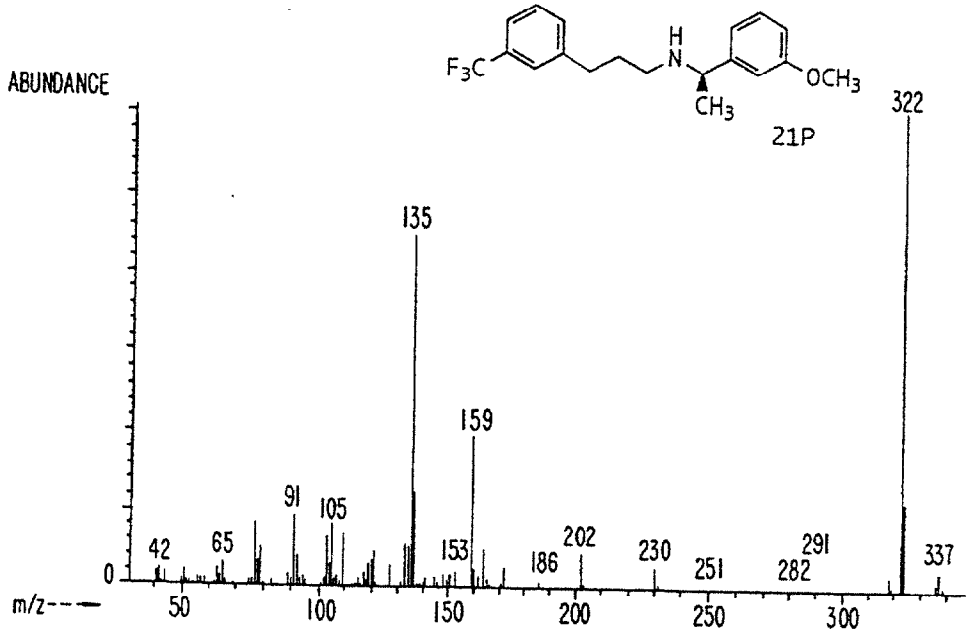

ABUNDANCE
135
159
91
105
42
65
153
186
202
230
251
282
291
322
337
0
m/z
50
100
150
200
250
300
F3C
H
N
CH3
OCH3
21P

FIG. 70.

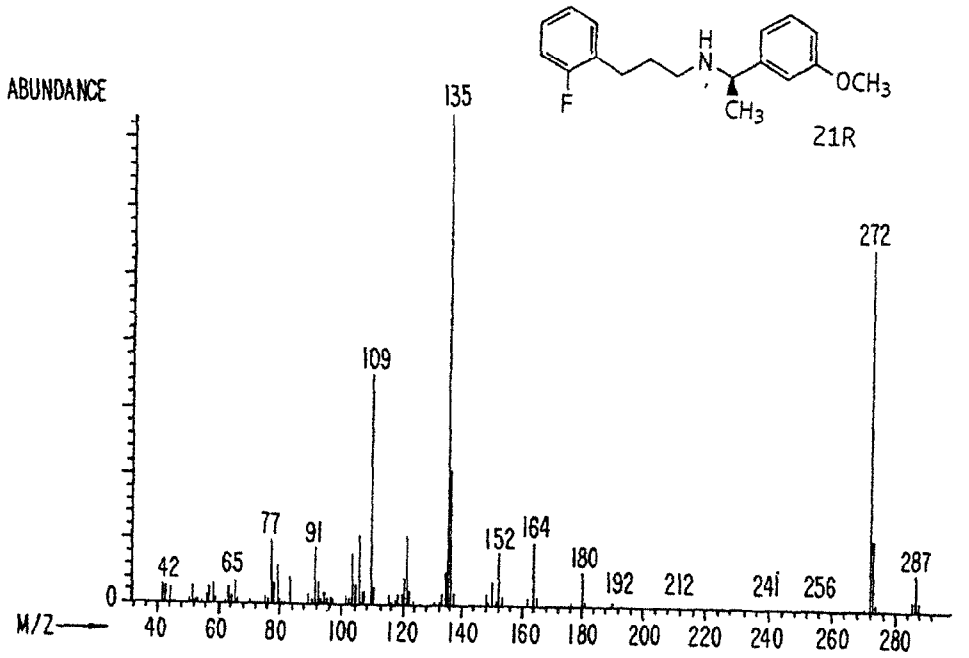

ABUNDANCE
M/Z
21R
F
H
N
CH3
OCH3
135
272
109
77
91
42
65
152
164
180
192
212
241
256
287
0
40
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 71.

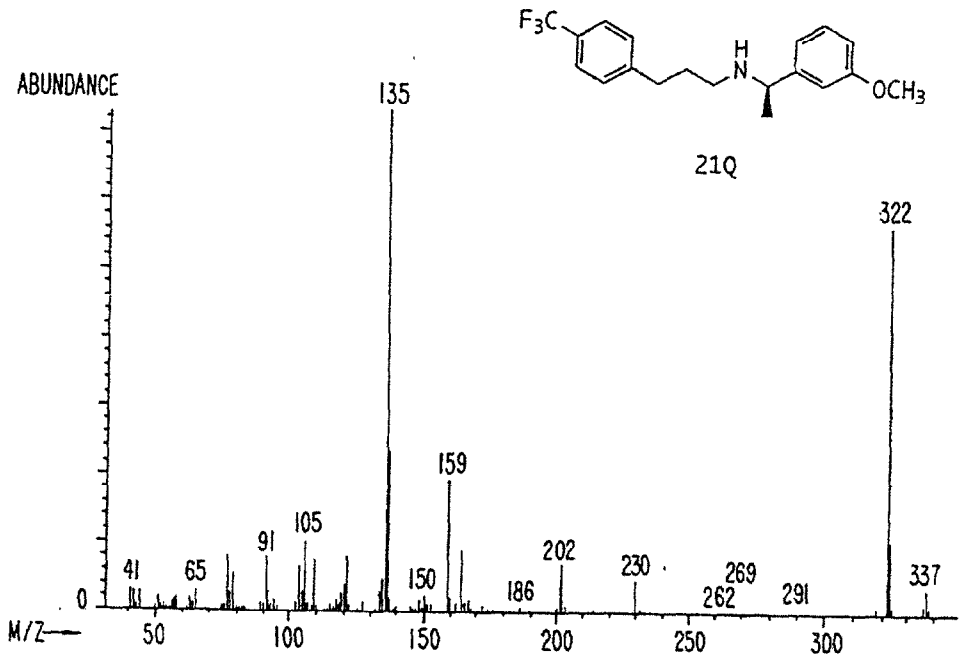

ABUNDANCE
M/Z
21Q
F3C
H
N
OCH3
135
322
159
105
91
41
65
150
186
202
230
262
269
291
337
0
50
100
150
200
250
300

FIG. 72.

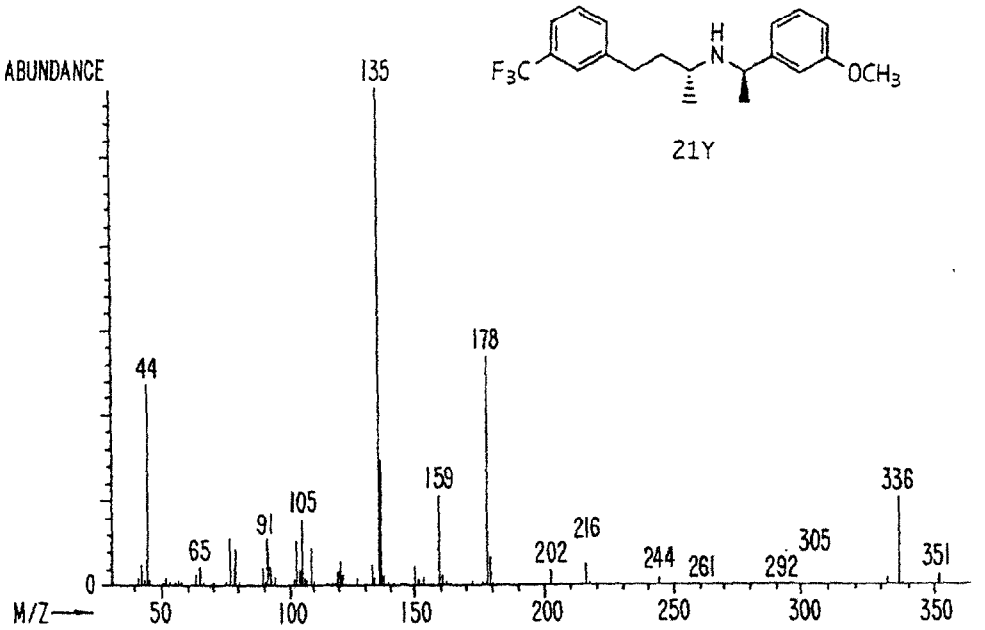

ABUNDANCE
135
178
44
159
336
105
91
65
216
202
244
261
292
305
351
0
M/Z
50
100
150
200
250
300
350
F3C
H
N
OCH3
21Y

FIG. 73.

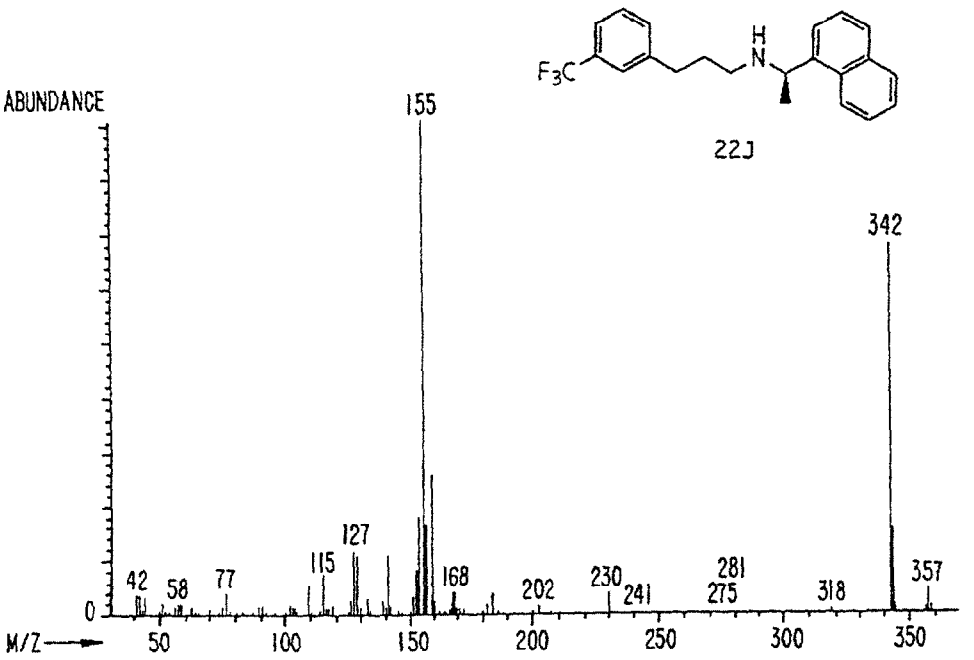

ABUNDANCE
155
342
127
115
42
58
77
168
202
230
241
281
275
318
357
0
M/Z
50
100
150
200
250
300
350
F3C
H
N
22J

FIG. 74.

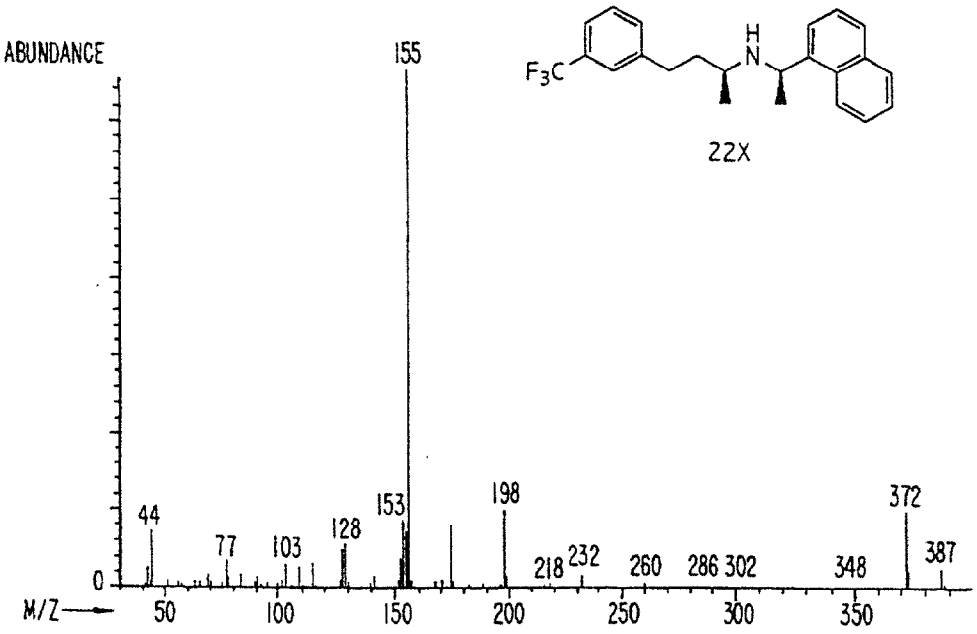

ABUNDANCE
155
F_3C
H
N
22X
44
77
103
128
153
198
218
232
260
286
302
348
372
387
0
M/Z
50
100
150
200
250
300
350

FIG. 75.

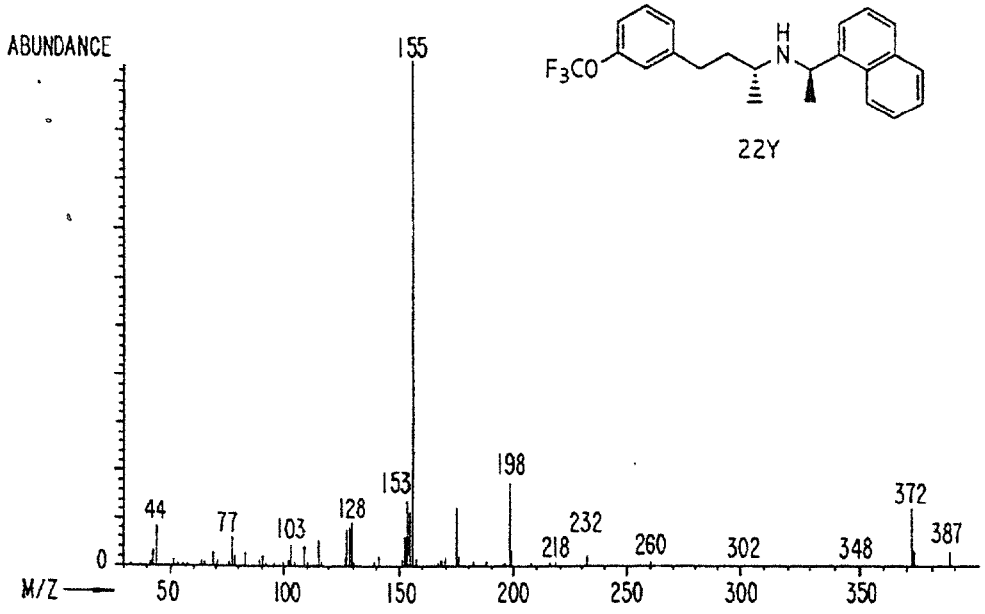

ABUNDANCE
155
F_3CO
H
N
22Y
44
77
103
128
153
198
218
232
260
302
348
372
387
0
M/Z
50
100
150
200
250
300
350

FIG. 76.

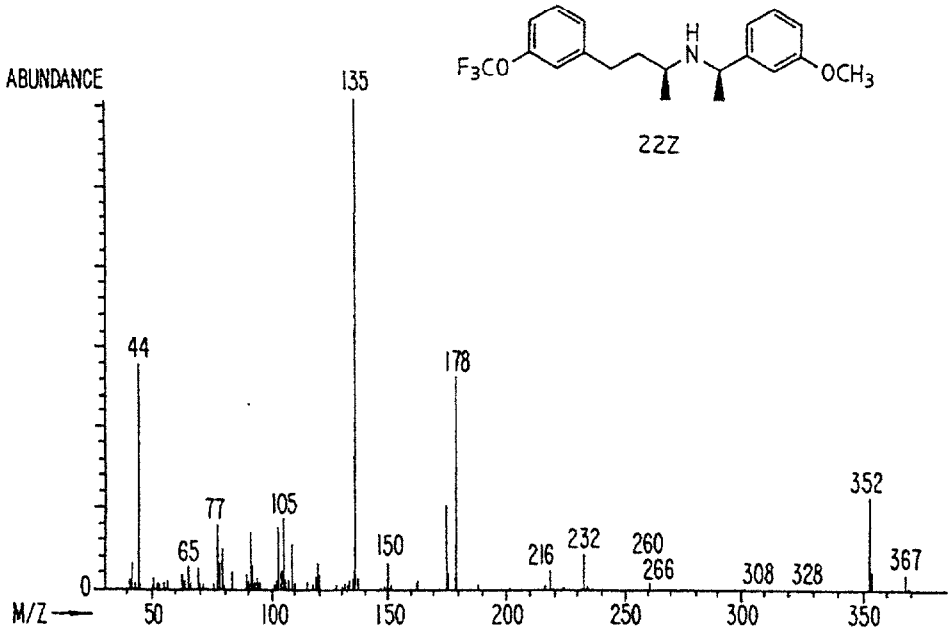

ABUNDANCE
135
44
178
77
105
65
150
216
232
260
266
308
328
352
367
0
M/Z
50
100
150
200
250
300
350
F3CO
H
N
OCH3
22Z

FIG. 77.

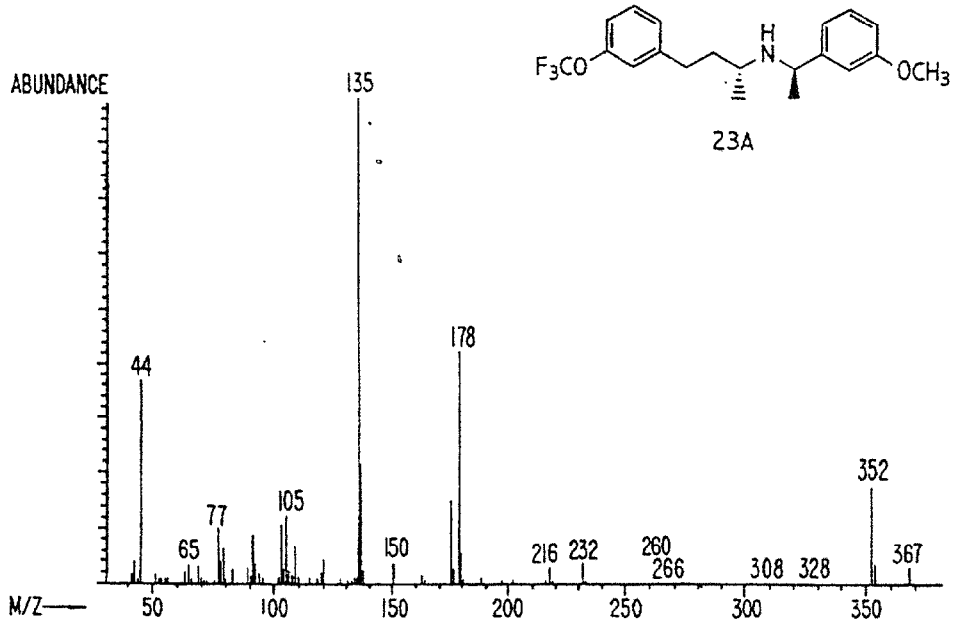

ABUNDANCE
135
44
178
77
105
65
150
216
232
260
266
308
328
352
367
M/Z
50
100
150
200
250
300
350
F3CO
H
N
OCH3
23A

FIG. 78

FIG. 79.

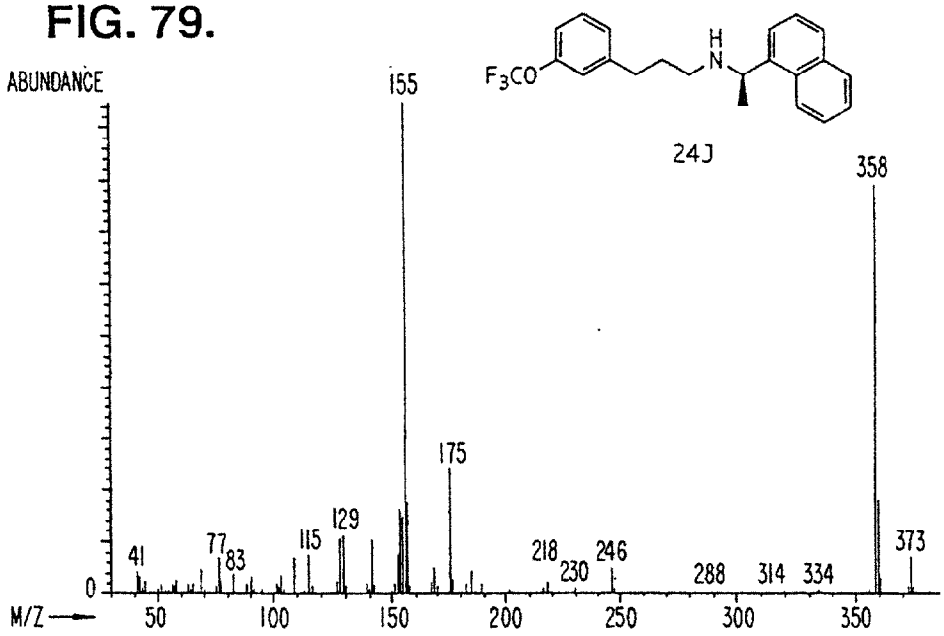

ABUNDANCE
155
358
175
129
115
77
83
41
218
230
246
288
314
334
373
0
M/Z
50
100
150
200
250
300
350
F3CO
H
N
24J

FIG. 80.

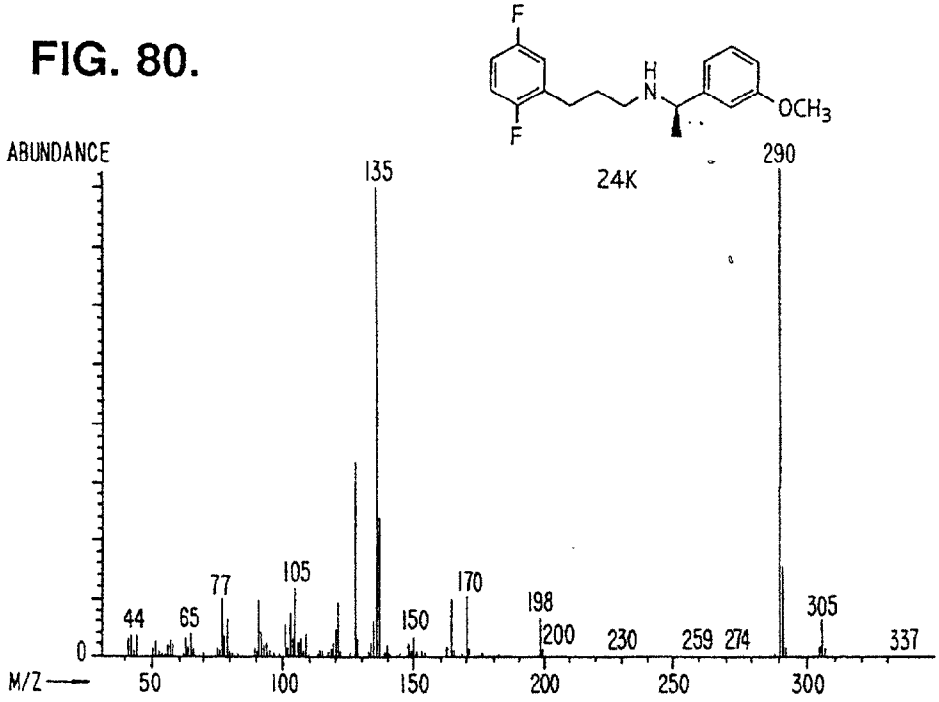

F
F
H
N
OCH3
24K
ABUNDANCE
135
290
77
105
170
198
44
65
150
200
230
259
274
305
337
0
M/Z
50
100
150
200
250
300

FIG. 81.

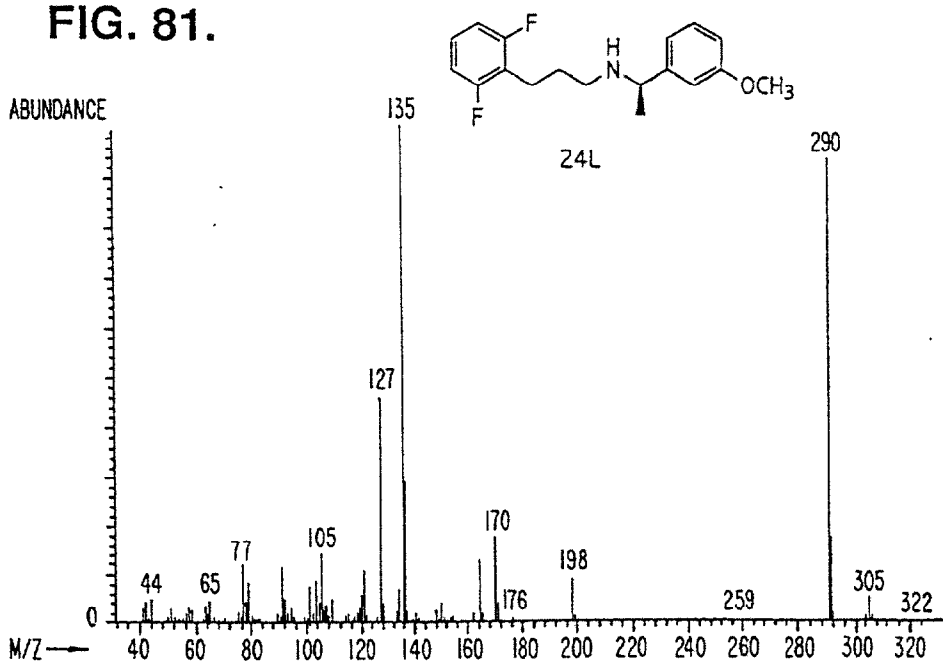
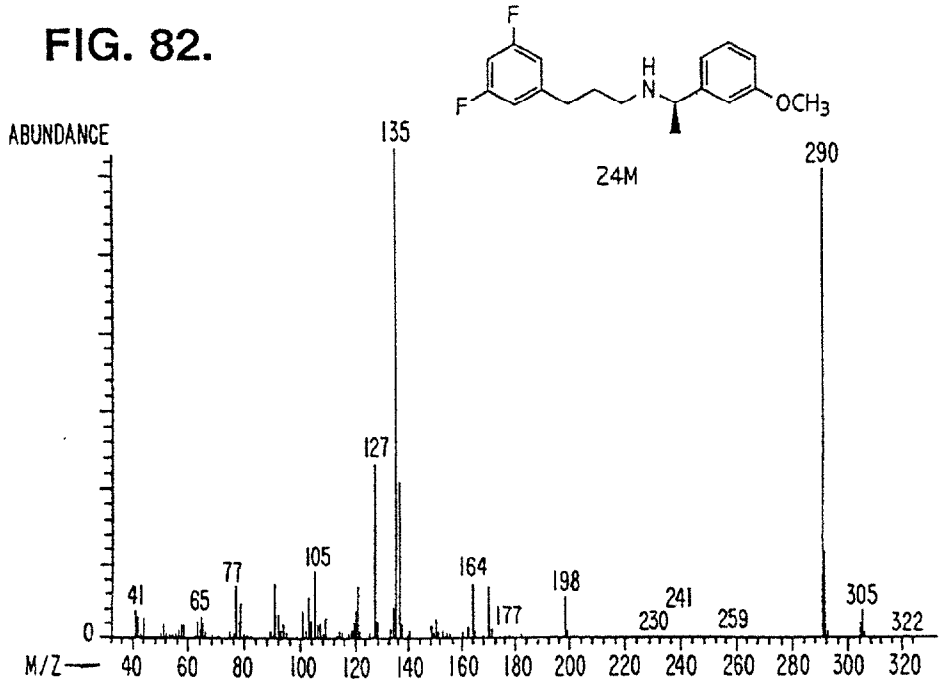

F
H
N
OCH3
F
24L
ABUNDANCE
135
290
127
170
105
77
198
44
65
176
259
305
322
0
M/Z
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320

FIG. 82.


F
H
N
OCH3
F
24M
ABUNDANCE
135
290
127
105
77
164
198
41
65
177
230
241
259
305
322
0
M/Z
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320

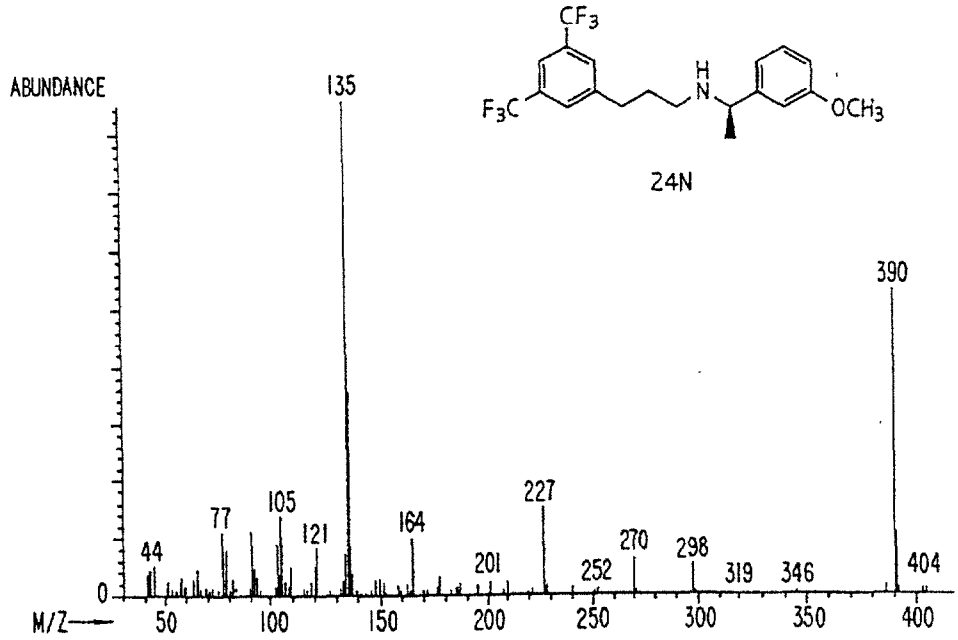

ABUNDANCE
135
390
227
105
77
121
164
44
201
252
270
298
319
346
404
0
M/Z
50
100
150
200
250
300
350
400
CF3
F3C
H
N
OCH3
24N

FIG. 83.

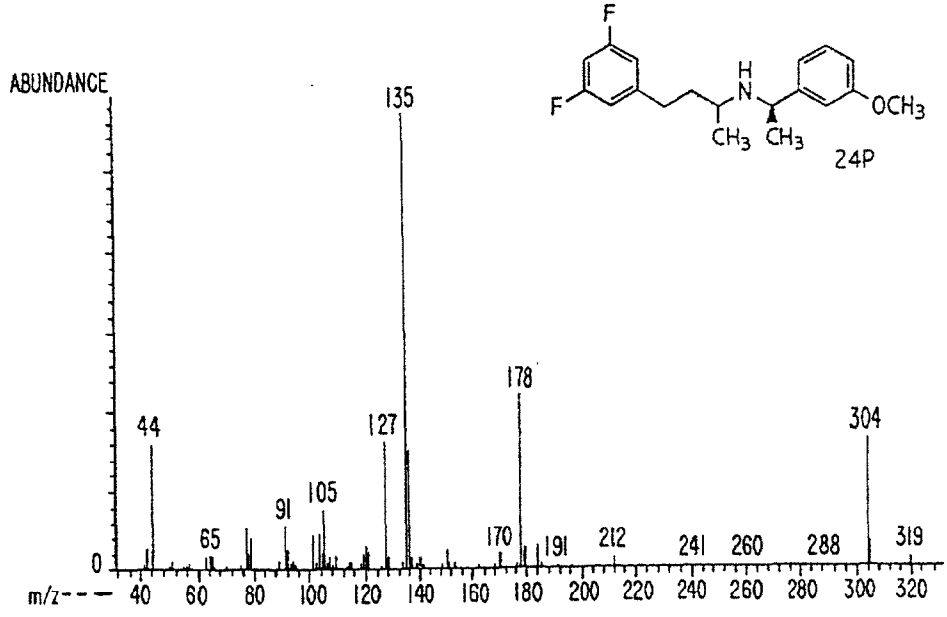

ABUNDANCE
135
178
44
127
304
105
91
65
170
191
212
241
260
288
319
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
F
F
H
N
OCH3
CH3
CH3
24P

FIG. 84.

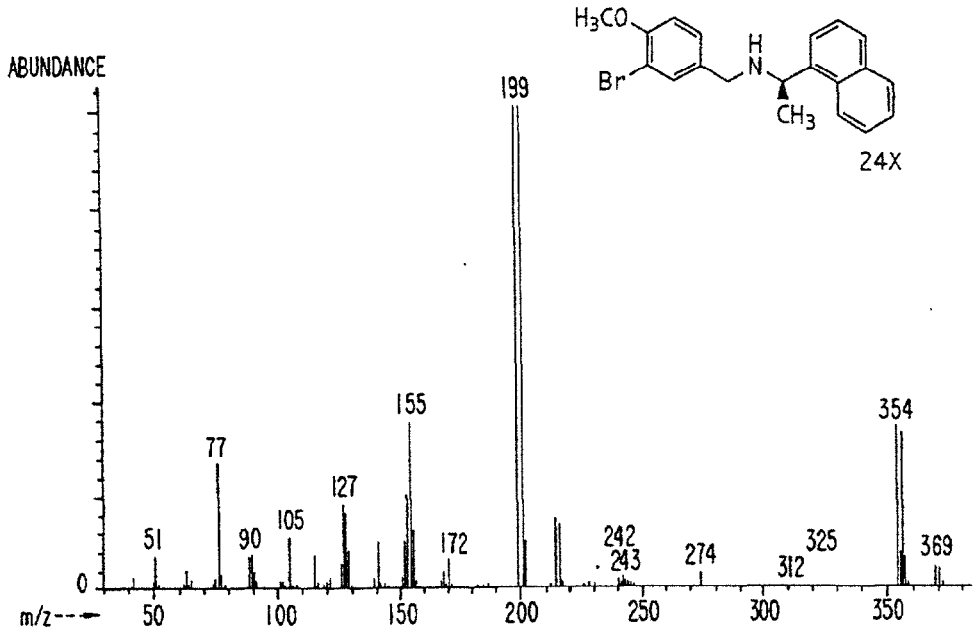

ABUNDANCE
H_3CO
Br
H
N
CH_3
24X
199
155
354
77
127
105
51
90
172
242
243
274
312
325
369
0
m/z
50
100
150
200
250
300
350

FIG. 85.

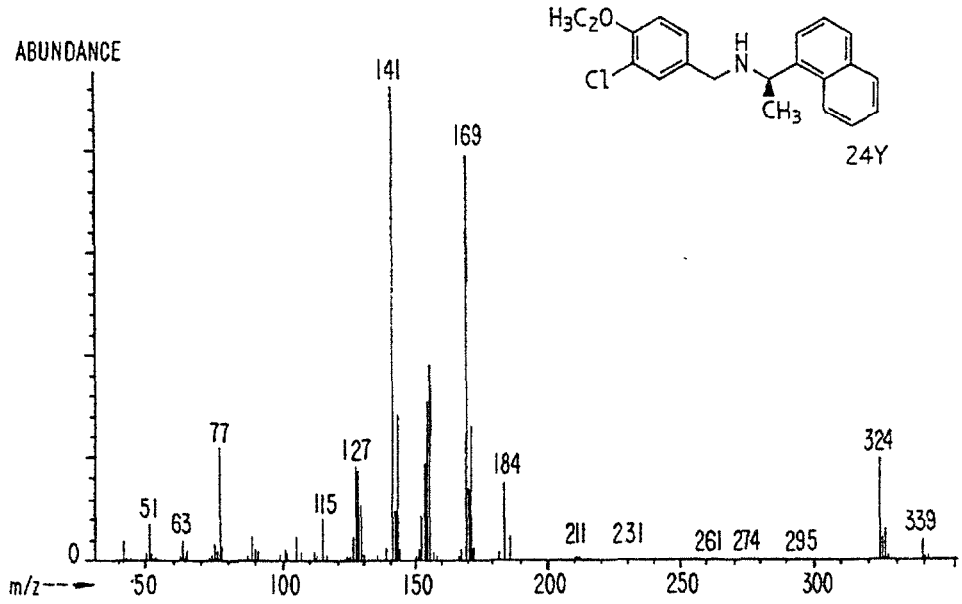

ABUNDANCE
H_3C_2O
Cl
H
N
CH_3
24Y
141
169
77
127
184
324
51
63
115
211
231
261
274
295
339
0
m/z
50
100
150
200
250
300

FIG. 86.

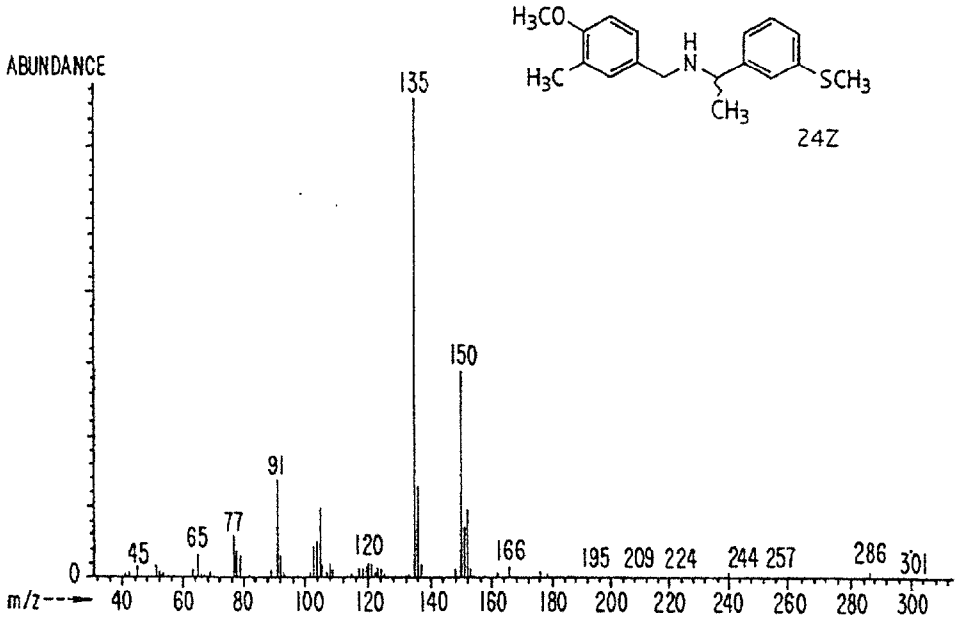

ABUNDANCE
135
150
91
77
65
45
120
166
195 209 224
244 257
286
301
0
m/z
40 60 80 100 120 140 160 180 200 220 240 260 280 300
H3CO
H3C
H
N
CH3
SCH3
24Z

FIG. 87.

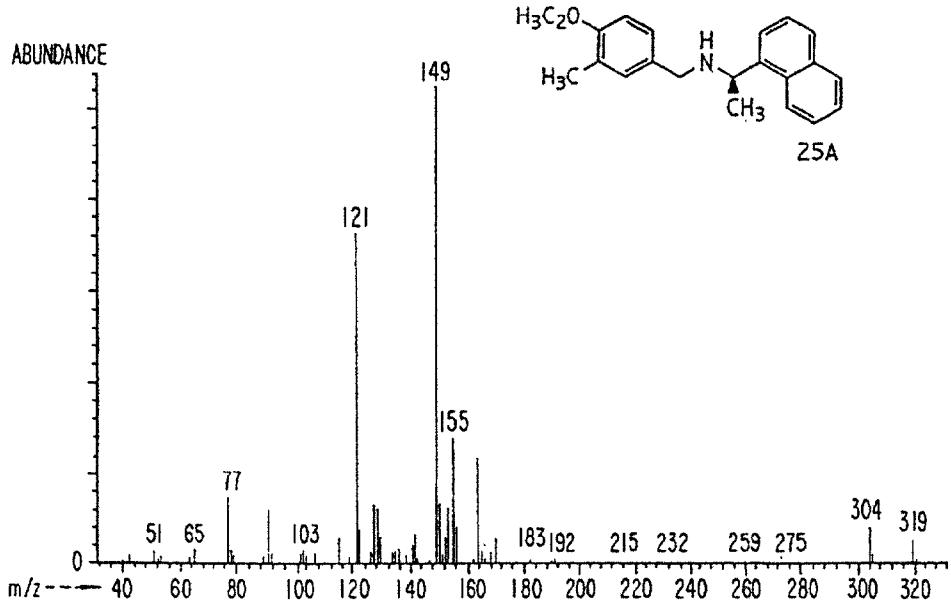

ABUNDANCE
149
121
155
77
51 65
103
183 192
215 232
259 275
304
319
0
m/z
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320
H3C2O
H3C
H
N
CH3
25A

FIG. 88.

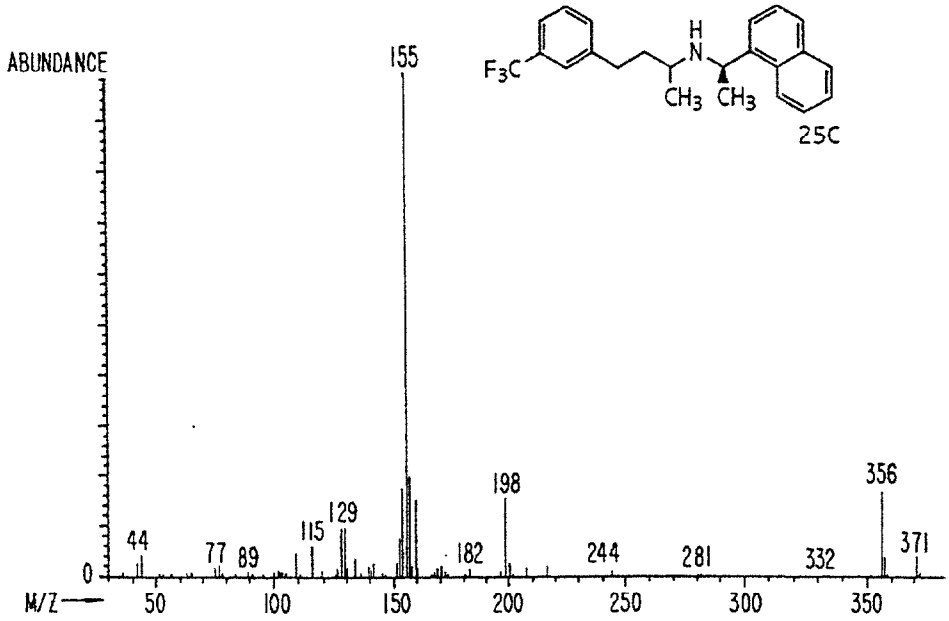

ABUNDANCE
155
198
356
129
115
44
77
89
182
244
281
332
371
0
M/Z
50
100
150
200
250
300
350
F3C
H
N
CH3
CH3
25C

FIG. 89.

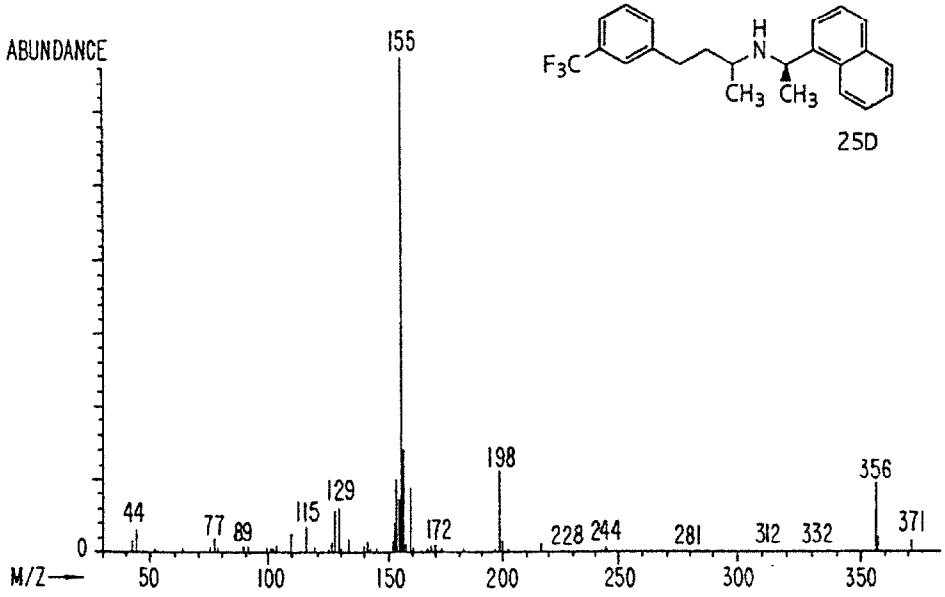

ABUNDANCE
155
198
356
129
115
44
77
89
172
228
244
281
312
332
371
0
M/Z
50
100
150
200
250
300
350
F3C
H
N
CH3
CH3
25D

FIG. 90.

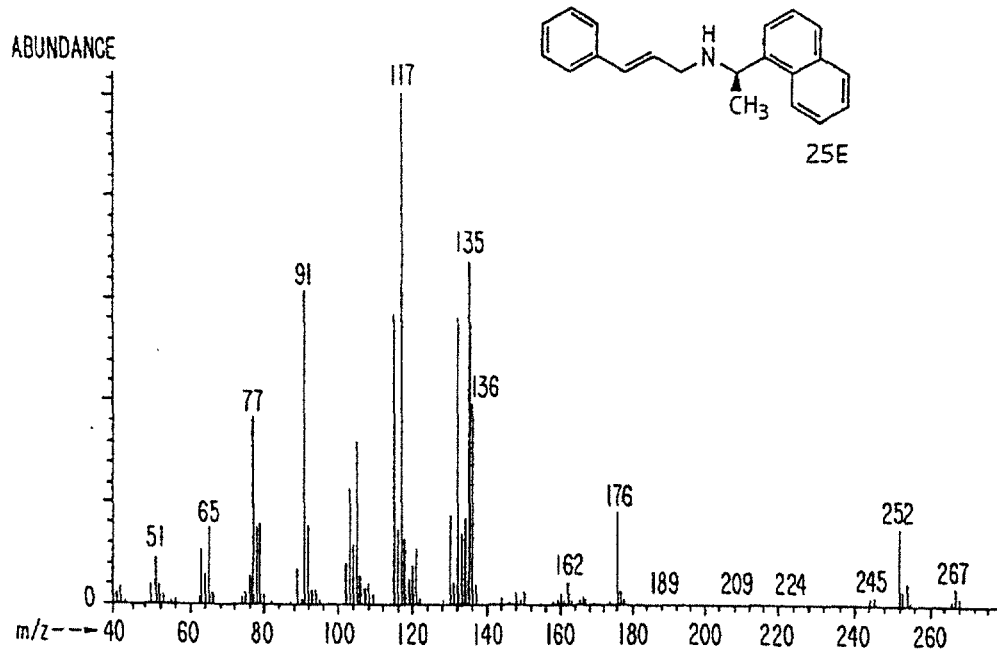

ABUNDANCE
117
135
91
136
77
176
65
252
51
162
189
209
224
245
267
0
m/z---→ 40
60
80
100
120
140
160
180
200
220
240
260
H
N
CH3
25E

FIG. 91.

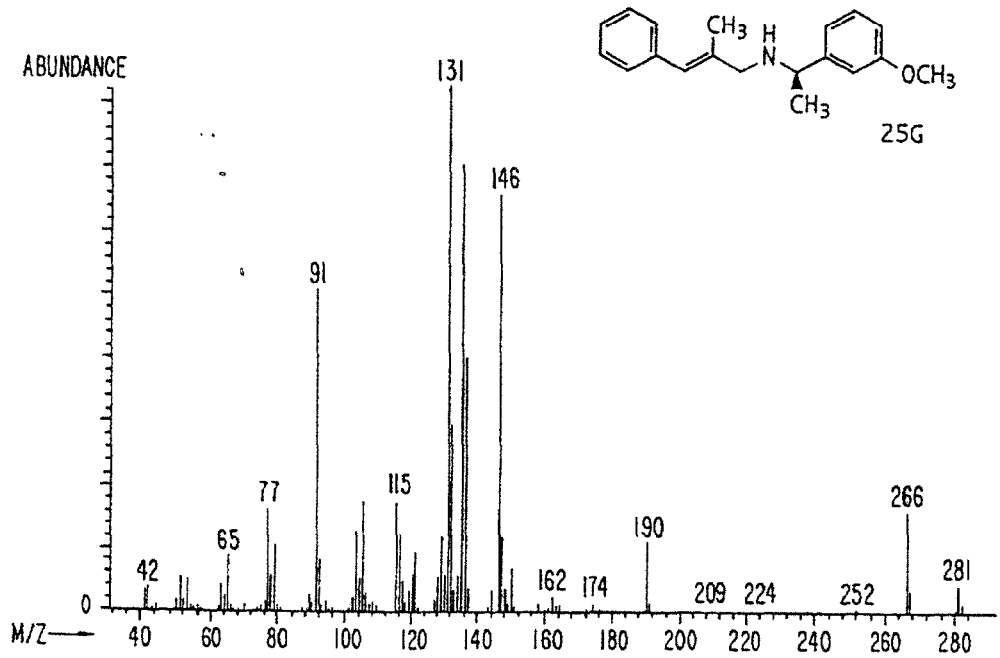

ABUNDANCE
131
146
91
77
115
266
190
65
42
162
174
209
224
252
281
0
M/Z→
40
60
80
100
120
140
160
180
200
220
240
260
280
CH3
H
N
OCH3
CH3
25G

FIG. 92.

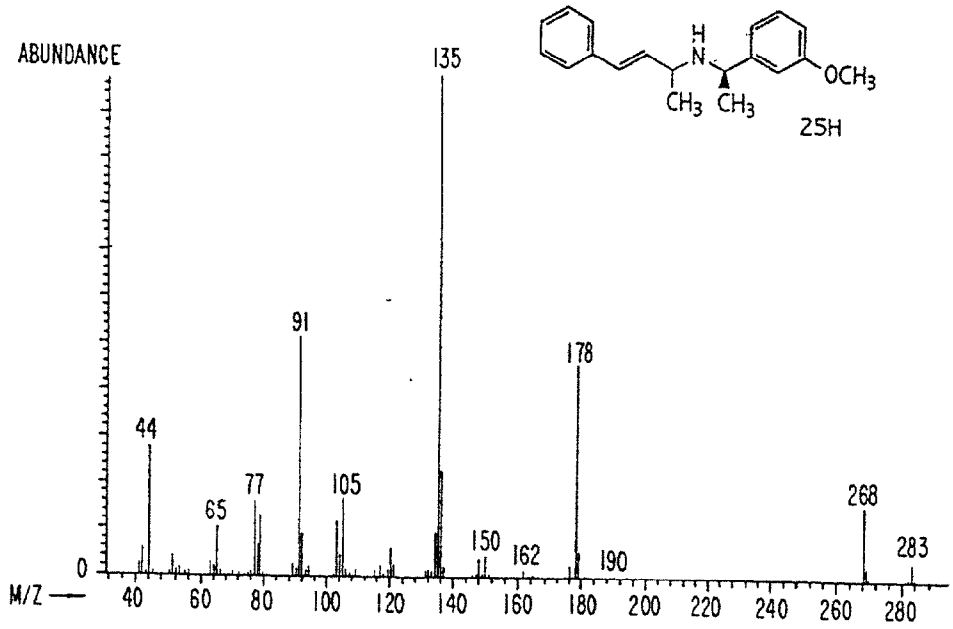

ABUNDANCE
135
91
178
44
77
105
65
150
162
190
268
283
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
H
N
OCH3
CH3 CH3
25H

FIG. 93.

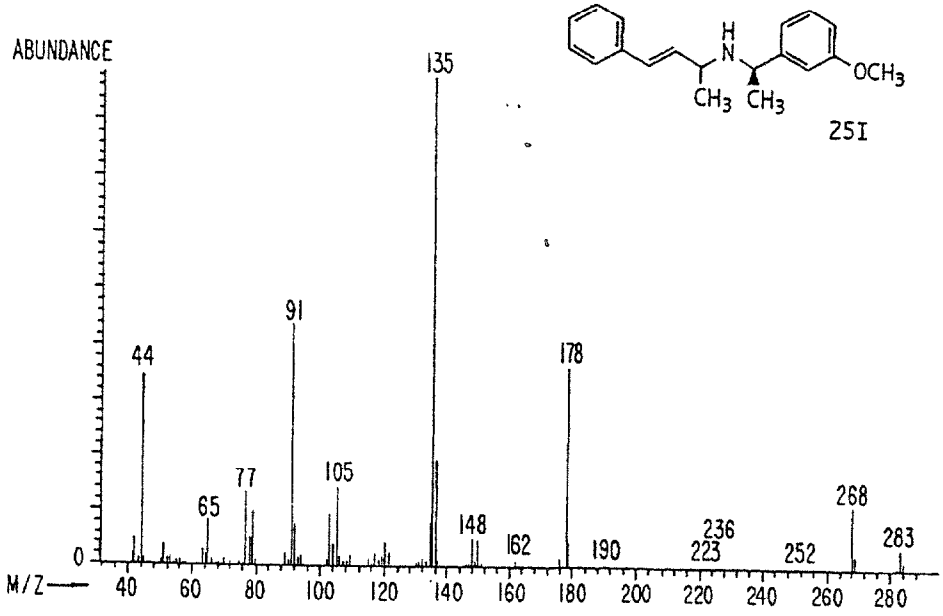

ABUNDANCE
135
91
44
178
77
105
65
148
162
190
236
223
252
268
283
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
H
N
OCH3
CH3 CH3
25I

FIG. 94.

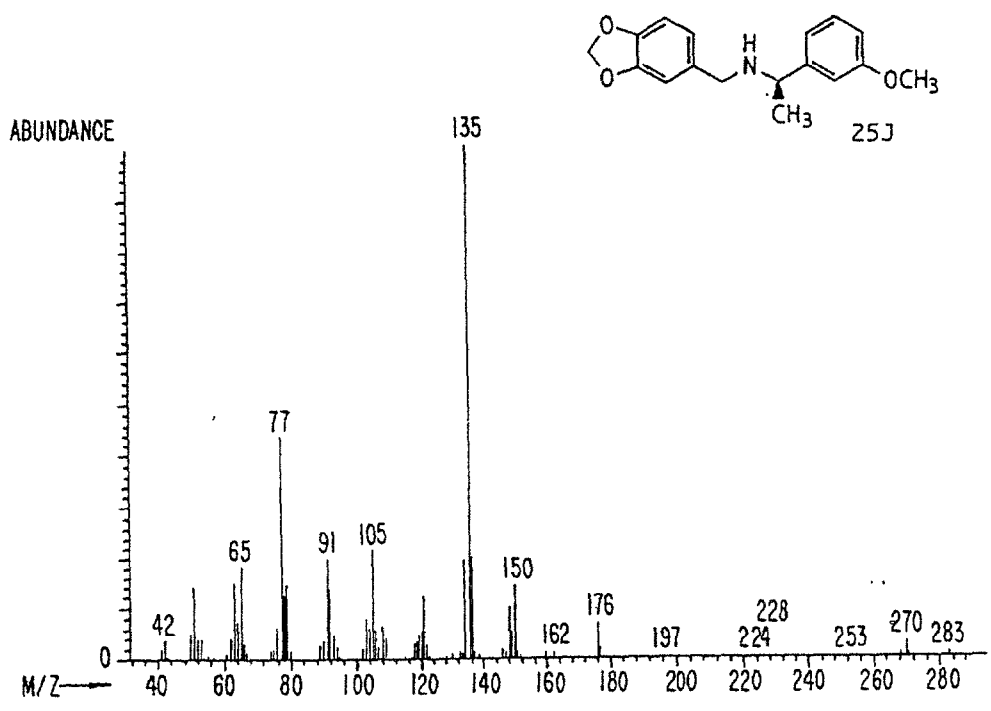
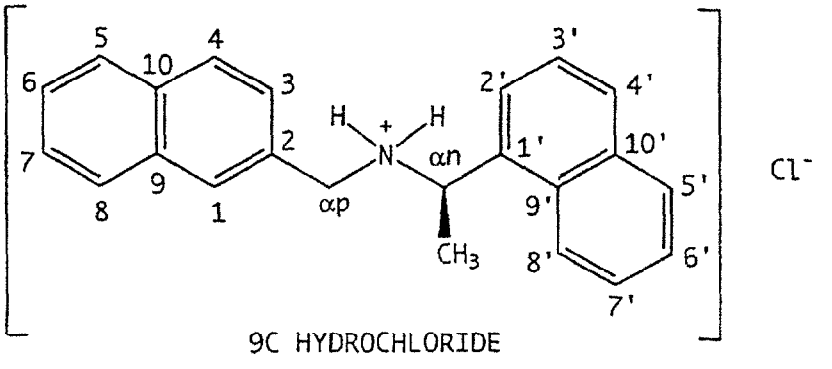

ABUNDANCE
135
77
65
91
105
150
176
42
162
197
224
228
253
270
283
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
O
O
H
N
OCH3
CH3
25J

FIG. 95.

FIG. 96.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:

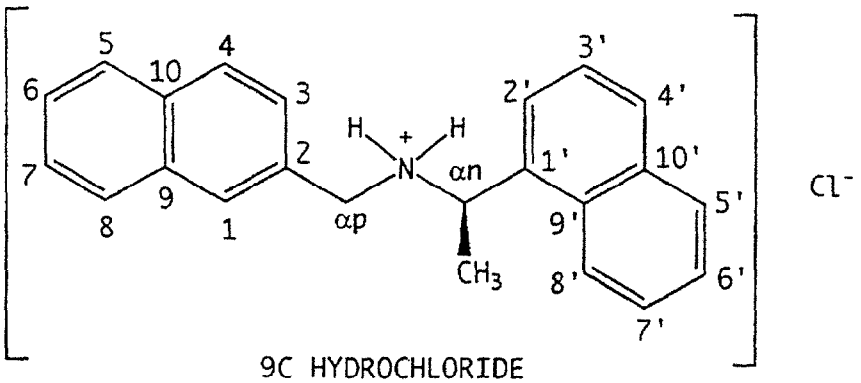


9C HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.85	d	J=6.8	aliph-CH_3
1H	4.05	d	J=13.2	-CH_2-
1H	4.16	d	J=13.4	-CH_2-
1H	5.06	q	J=7.0	aliph-CH-
8H	7.21-7.47	m	n.a.	
1H	7.54	d	J=8.8	
2H	7.65-7.73	m	n.a.	
2H	7.89	d	J=7.8	
1H	8.43	d	J=7.2	
1H	10.47	bs	n.a.	aliph-NH_2+
1H	10.84	bs	n.a.	aliph-NH_2+

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:



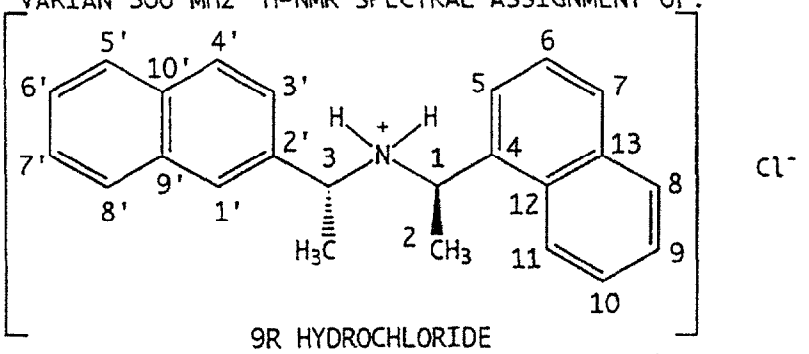
9C HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
21.18	CH_3	aliph-CH_3
48.5	CH_2	-CH_2-
51.46	CH	-CH-
121.42	CH	RIGHT SIDE
125.21	CH	RIGHT SIDE
125.99	CH	LEFT SIDE
126.04	CH	RIGHT SIDE
126.15	CH	RIGHT SIDE
126.63	CH	LEFT SIDE
126.69	CH	LEFT SIDE
126.91	Q	LEFT SIDE
127.37	CH	RIGHT SIDE
127.45	CH	LEFT SIDE
127.93	CH	LEFT SIDE
128.52	CH	LEFT SIDE
129.04	CH	LEFT SIDE
129.24	CH	RIGHT SIDE
130.32	Q	RIGHT SIDE
130.83	CH	RIGHT SIDE
132.23	Q	RIGHT SIDE
132.59	Q	LEFT SIDE
133.15	Q	LEFT SIDE
133.66	Q	RIGHT SIDE

FIG. 97.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



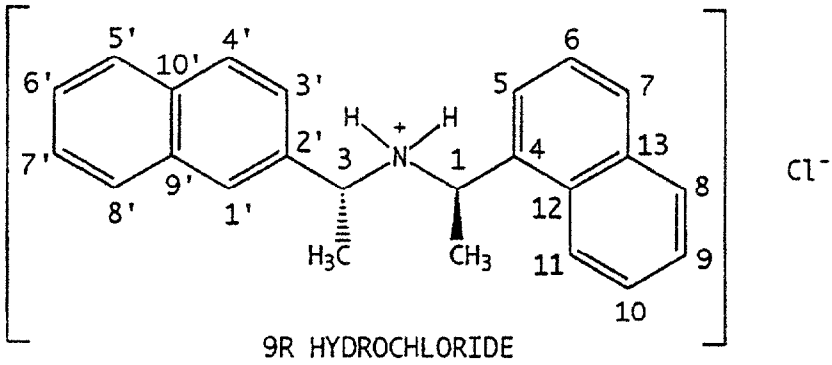
NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.97	d	J=6.8	aliph-CH_3
3H	2.03	d	J=6.8	aliph-CH_3
1H	4.17	q	J=6.9	aliph-CH-
1H	4.81	q	J=6.9	aliph-CH-
2H	6.77-6.85	m	n.a.	
1H	7.14	bs	n.a.	
4H	7.33-7.52	m	n.a.	
6H	7.74-7.94	m	n.a.	
1H	8.69	bs	n.a.	
1H	10.82	bs	n.a.	aliph-NH_2+
1H	10.89	bs	n.a.	aliph-NH_2+

FIG. 98.

FIG. 99.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:

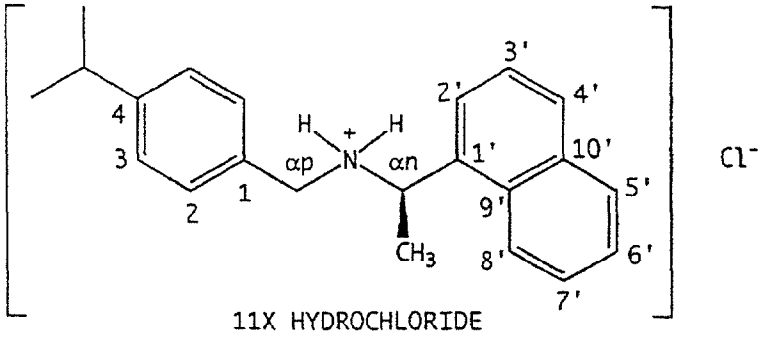


9R HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
20.83	CH_3	aliph-CH_3
21.87	CH_2	aliph-CH_3
51.37	CH	-CH_2-
57.27	CH	-CH-
121.40	CH	
124.65	CH	
125.50	CH	
125.82	CH	
126.09	CH	
126.22	CH	
126.62	CH	
127.49	CH	
128.01	CH	
128.76	CH	
129.08	CH	
129.25	CH	
130.19	Q	
132.74	Q	
132.78	Q	
132.95	Q	
133.27	Q	
133.53	Q	

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:

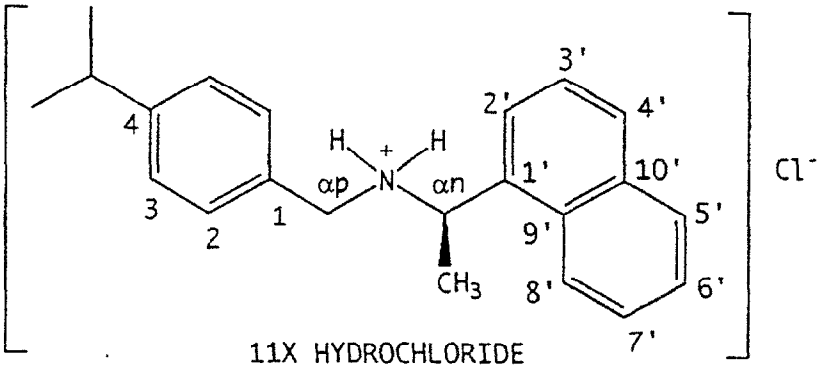


NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
6H	1.17	d	J=7.1	$-CH(C\underline{H}_3)_2$
3H	1.86	d	J=6.8	aliph-CH_3
1H	2.84	p	J=7.0	$-C\underline{H}(CH_3)_2$
1H	3.88	d	J=13.3	-CH2-
1H	3.97	d	J=13.3	-CH2-
1H	5.02	q	J=6.8	aliph-CH-
1H	7.03	d	J=8.1	3
1H	7.17	d	J=8.1	2
3H	7.40-7.54	m	n.a.	
1H	7.68	dd	$J_1=J_2=7.9$	3'
1H	7.89	d	J=8.3	4' OR 5'
1H	7.91	d	J=8.1	4' OR 5'
1H	8.41	d	J=7.1	2'
1H	10.38	bs	n.a.	aliph-NH_2+
1H	10.77	bs	n.a.	aliph-NH_2+

FIG. 100.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:

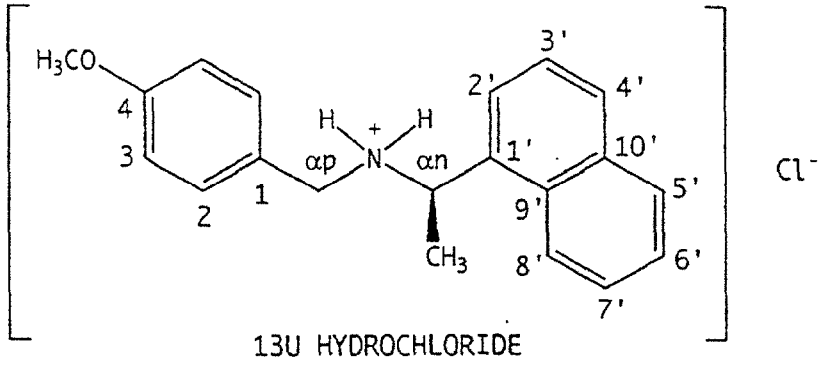


NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
21.33	CH_3	aliph-CH_3
23.58	CH_3	-CH($C\underline{H}_3$)$_2$
33.66	CH	arom-CH
48.27	CH_2	-CH_2-
51.52	CH	aliph-CH-
121.57	CH	
---	---	
---	---	
125.17	CH	
125.94	CH	
126.05	CH	
126.65	CH	
127.05	Q	
129.10	CH	
130.02	CH	
130.39	Q	
130.90	CH	
132.43	Q	
133.71	Q	
149.84	Q	

FIG. 101.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



13U HYDROCHLORIDE

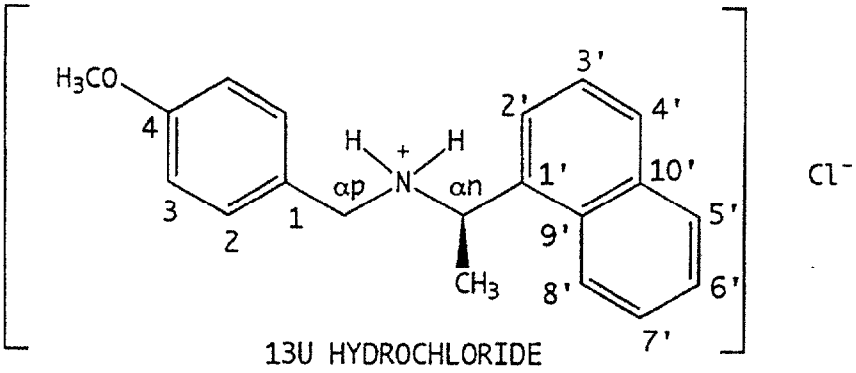
NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.92	d	J=6.6	aliph-CH_3
3H	3.64	s	n.a.	-OCH_3
1H	3.85	d	J=13.4	-CH_2-
1H	3.93	d	J=13.5	-CH_2-
1H	5.04	q	J=6.9	aliph-CH-
2H	6.72 (6.71 calc)	d	J=8.3	3
2H	7.21 (7.10 calc)	d	J=8.0	2
2H	7.47-7.55	m	n.a.	
1H	7.60	d	J=8.3	
1H	7.69	dd	J=7.9/7.5	3'
1H	7.90	d	J=7.9	4' OR 5'
1H	7.92	d	J=7.7	4' OR 5'
1H	8.42	d	J=7.3	2'
1H	10.35	bs	n.a.	aliph-NH_2+
1H	10.73	bs	n.a.	aliph-NH_2+

FIG. 1O2.

FIG. 103.

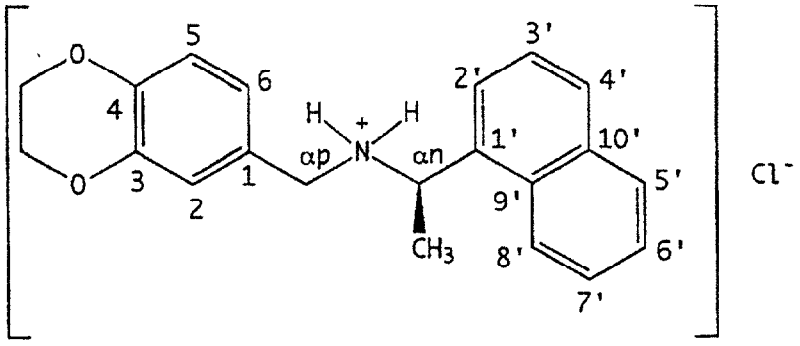
VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:



NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
21.16	CH_3	aliph-CH_3
47.86	CH_2	-CH_2-
51.28	CH	-CH-
54.94	CH_3	O-CH_3
113.82	CH	3'
121.47	CH	
121.58	Q	LEFT SIDE arom-C-CH_2NH_2
---	---	
125.03	CH	
125.91	CH	
125.94	CH	
126.68	CH	
129.06	CH	
---	---	
130.25	Q	
---	---	
---	---	
132.27	CH	2'
133.63	Q	NH_2-CH_2-C-naphthyl
159.95	Q	arom-C-OCH_3

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



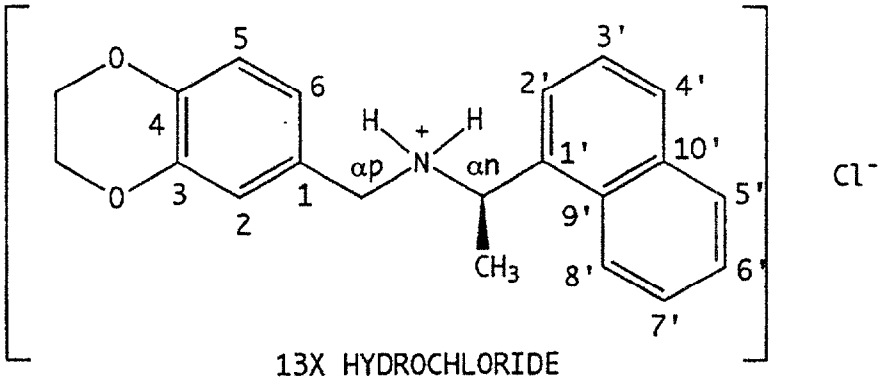
13X HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.91	d	J=6.7	aliph-CH_3
1H	3.75	d	J=13.3	-CH_2-
1H	3.91	d	J=13.3	-CH_2-
4H	4.10	m	n.a.	-O-CH_2CH_2-O-
1H	5.03	q	J=7.0	aliph-CH-
3H	6.70-6.80	m	n.a.	
4H	7.47-7.56	m	n.a.	
1H	7.66	dd	J_1=J_2=8.1	3'
1H	7.90	d	J=7.4	4' OR 5'
1H	7.91	d	J=7.4	4' OR 5'
1H	8.28	d	J=7.2	2'
1H	10.34	bs	n.a.	aliph-NH_2+
1H	10.83	bs	n.a.	aliph-NH_2+

FIG. 104.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:



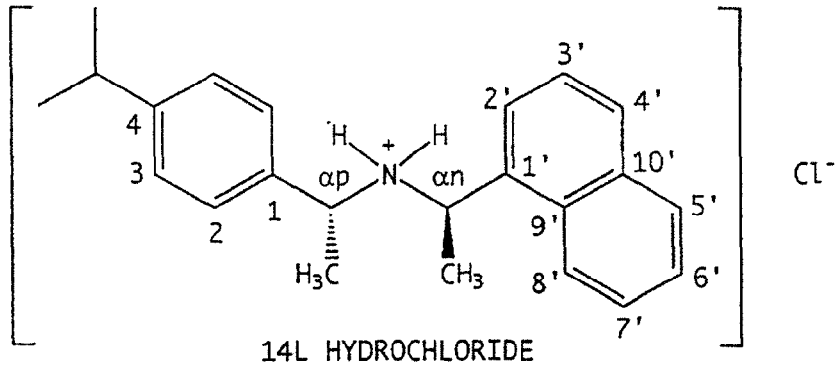
13X HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
20.87	CH_3	aliph-CH_3
47.87	CH_2	-CH_2-
51.16	CH	-CH-
63.86	CH_2	-O-$\underline{C}H_2$-CH_2-O-
64.09	CH_2	-O-CH_2-$\underline{C}H_2$-O-
117.40	CH	
119.66	CH	
121.45	CH	
122.61	Q	
123.67	CH	
124.83	CH	
125.85	CH	
125.96	CH	
126.76	CH	
129.09	CH	
129.22	CH	
130.31	Q	
132.17	Q	
133.67	Q	
143.28	Q	-O-$\underline{C}$-arom
144.17	Q	-O-$\underline{C}$-arom

FIG. 105.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



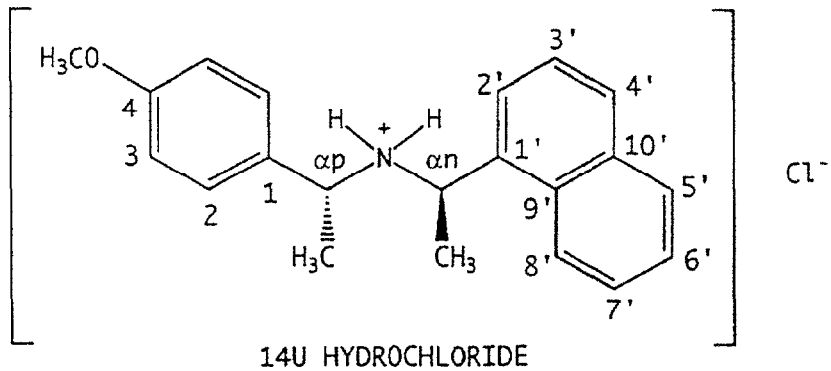
14L HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-10 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 10-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.236	d	J=7.0	$-CH(C\underline{H}_3)_2$
3H	1.242	d	J=6.9	$-C\underline{H}(CH_3)_2$
3H	1.84	d	J=6.8	aliph-CH_3
3H	1.86	d	J=6.8	aliph-CH_3
1H	2.88	p	J=6.8	$-C\underline{H}(CH_3)_2$
1H	3.97	bq	J=6.7	aliph-CH-
1H	4.77	bq	J=6.9	aliph-CH-
1H	6.95	d	J=8.2	H-3'
1H	7.05	d	J=8.3	H-2'
1H	7.26	dd	J1=J2=7.1	
1H	7.48	dd	J1=J2=7.7	
1H	7.68	dd	$J_1=J_2=7.7$	
1H	7.90	d	J=7.7	
1H	7.91	d	J=7.9	
1H	8.24	bd	J=6.5	
2H	10.71	bs	n.a.	aliph-NH_2+

FIG. 106.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



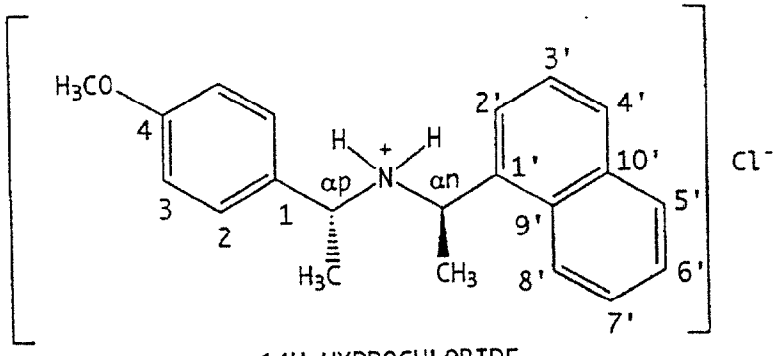
14U HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-10 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 10-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.93	d	J=6.8	aliph-CH_3
3H	1.94	d	J=6.7	aliph-CH_3
3H	3.80	s	n.a.	-OCH_3
1H	4.01	q	J=7.0	aliph-CH-
1H	4.82	q	J=6.9	aliph-CH-
2H	6.73	d	J=8.8	3
2H	7.07	d	J=8.6	2
1H	7.15	bd	J=7.3	8'
1H	7.33	dd	$J_1=J_2=7.7$	7'
1H	7.49	dd	$J_1=J_2=7.6$	6'
1H	7.70	dd	$J_1=J_2=7.8$	3'
1H	7.90	d	J=8.1	4' OR 5'
1H	7.91	d	J=8.0	4' OR 5'
1H	8.44	bd	J=5.4	2'
2H	10.65	bs	n.a.	aliph-NH_2+

FIG. 107.

VARIAN 75MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:



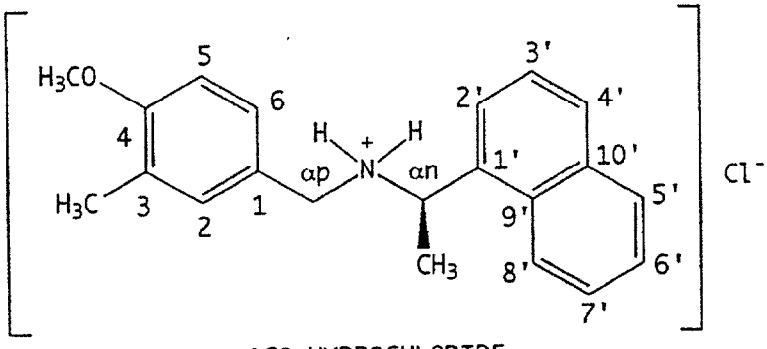
14U HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
21.11	CH_3	aliph-CH_3
21.93	CH_3	aliph-CH_3
51.29	CH	-CH-
55.30	CH_3	O-CH_3
56.61	CH	-CH-
114.30	CH	3'
121.77	CH	
---	---	
125.38	CH	
125.91	CH	
126.17	CH	
126.40	CH	
127.88	Q	
128.96	CH	
128.99	CH	
128.79	CH	
130.22	Q	
---	---	
132.88	Q	
133.70	Q	
159.97	Q	arom-C-OCH_3

FIG. 108.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



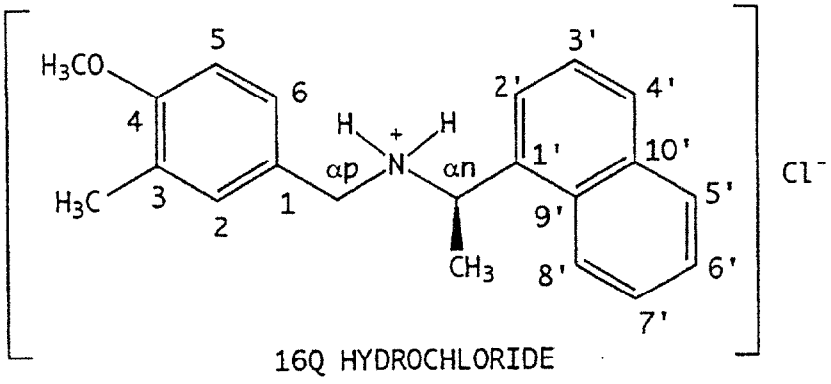
16Q HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.85	d	J=6.7	aliph-CH_3
3H	2.01	s	n.a.	arom-CH_3
3H	3.77	s	n.a.	-OCH_3
1H	3.80	d	J=13.1	-CH_2-
1H	3.97	d	J=13.2	-CH_2-
1H	5.00	q	J=6.7	aliph-CH-
1H	6.69 (6.59 calc)	d	J=8.4	5
1H	6.78 (6.90 calc)	bs	n.a.	2'
1H	7.22 (6.88 calc)	bd	J=8.2	6'
3H	7.44-7.57	m	n.a.	
1H	7.70	dd	J=7.6/7.8	3'
1H	7.91	d	J=8.1	4' OR 5'
1H	7.92	d	J=8.1	4' OR 5'
1H	8.44	d	J=7.1	2'
1H	10.35	bs	n.a.	aliph-NH_2+
1H	10.70	bs	n.a.	aliph-NH_2+

FIG. 109.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:

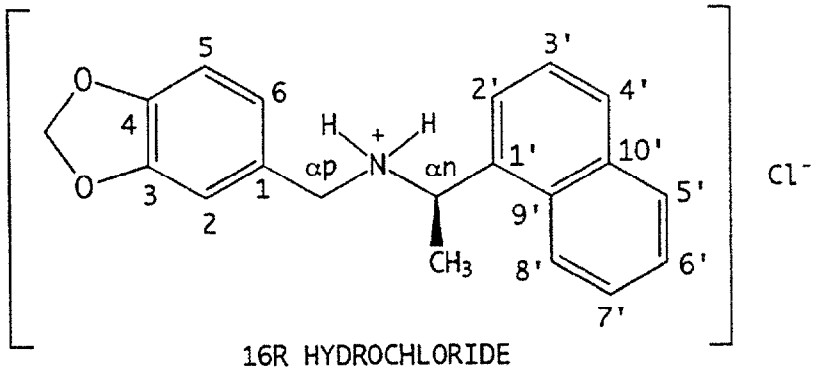


NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
15.74	CH_3	arom-CH_3
22.32	CH_3	aliph-CH_3
47.85	CH_2	-CH_2-
51.01	CH	-CH-
55.09	CH_3	O-CH_3
109.81	CH	5'
121.56	CH	RIGHT SIDE
121.01	Q	LEFT SIDE arom-C-CH_2NH_2
---	---	
125.13	CH	RIGHT SIDE
125.90	CH	
126.03	CH	RIGHT SIDE
126.61	CH	RIGHT SIDE
129.05	CH	RIGHT SIDE
129.72	CH	RIGHT SIDE
130.31	Q	RIGHT SIDE
---	---	
132.44	Q	RIGHT SIDE
133.23	CH	6'
133.68	Q	NH_2-CH_2-C-naphthyl
158.16	Q	arom-C-OCH_3

FIG. 11O.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



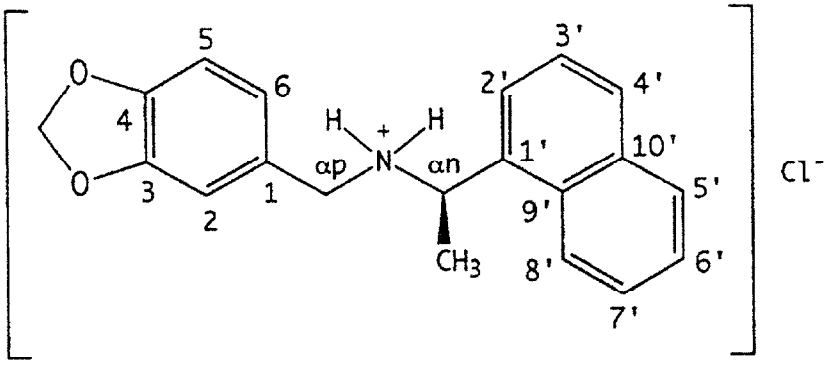
16R HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-10 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 10-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.88	d	J=6.8	aliph-CH_3
1H	3.85	d	J=13.4	-CH_2-
1H	3.94	d	J=13.4	-CH_2-
1H	5.06	q	J=6.7	aliph-CH-
2H	5.90	dd	J1=2.2;J2=1.4	-O-CH_2-O-
2H	6.65	s	n.a.	
1H	6.85	s	n.a.	
2H	7.50-7.58	m	n.a.	
2H	7.63-7.70	m	n.a.	
1H	7.92	d	J=8.1	4' OR 5'
1H	7.94	d	J=9.5	4' OR 5'
1H	8.12	d	J=6.7	2'
1H	10.37	bs	n.a.	aliph-NH_2+
1H	10.80	bs	n.a.	aliph-NH_2+

FIG. 111.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:



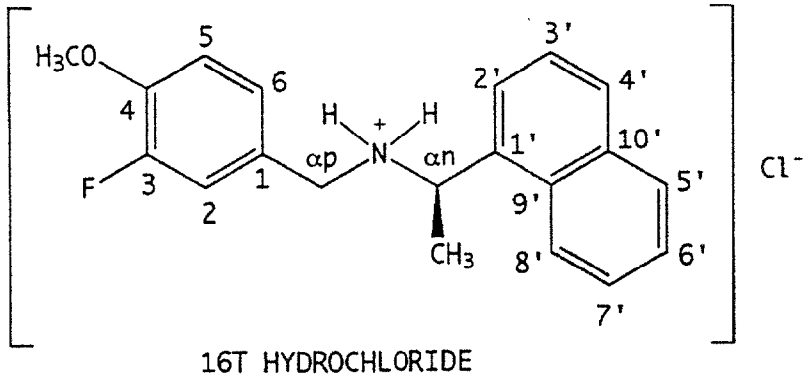
16R HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
21.20	CH_3	aliph-CH_3
48.39	CH_2	-CH_2-
51.26	CH	-CH-
101.16	CH_2	-O-$\underline{C}H_2$-O-
108.19	CH	
110.11	CH	
121.25	CH	
123.18	Q	
124.13	CH	
124.21	CH	
125.49	CH	
126.05	CH	
126.89	CH	
129.03	CH	
129.88	CH	
130.22	Q	
131.93	Q	
133.63	Q	
147.77	Q	-O-$\underline{C}$-arom
148.26	Q	-O-$\underline{C}$-arom

FIG. 112.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



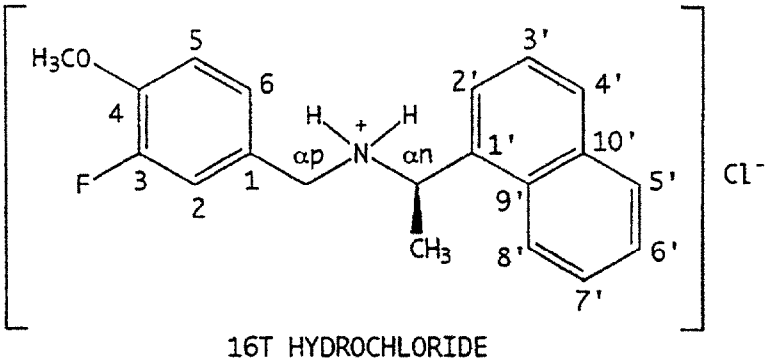
16T HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-10 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 10-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.89	d	J=6.6	aliph-CH_3
3H	3.80	s	n.a.	-OCH_3
1H	3.85	d	J=13.7	-CH_2-
1H	3.95	d	J=13.3	-CH_2-
1H	5.09	q	J=6.6	aliph-CH-
1H	6.84	t	J=8.2	
2H	7.01-7.08	m	n.a.	
2H	7.53-7.56	m	n.a.	
2H	7.64-7.72	m	n.a.	
2H	7.93	d	J=7.6	4' OR 5'
1H	8.19	d	J=7.1	2'
1H	10.41	bs	n.a.	aliph-NH_2+
1H	10.82	bs	n.a.	aliph-NH_2+

FIG. 113.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:



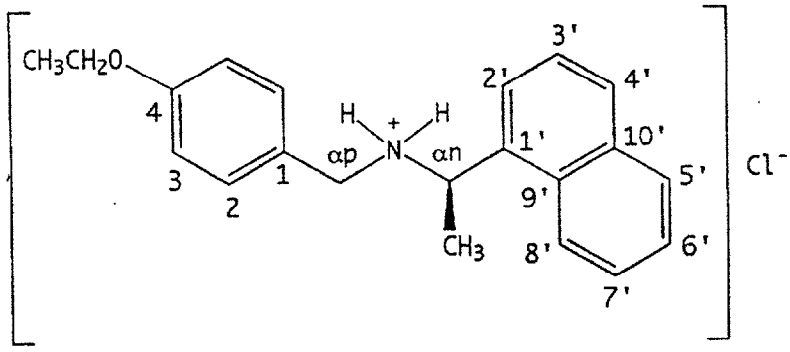
16T HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
20.71	CH_3	aliph-CH_3
47.67	CH_2	-CH_2-
51.47	CH	-CH-
55.91	CH_3	O-CH_3
113.12	CH	
113.13	CH	
117.99	CH	
118.24	CH	
121.30	CH	
122.22	Q	
122.31	Q	
124.61	CH	
125.76	CH	
126.16	CH	
126.92	CH	
127.00	CH	
129.17	CH	
129.47	CH	
130.29	Q	
131.92	Q	
133.73	Q	
148.21	Q	
148.35	Q	
150.01	Q	
153.29	Q	

FIG. 114.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



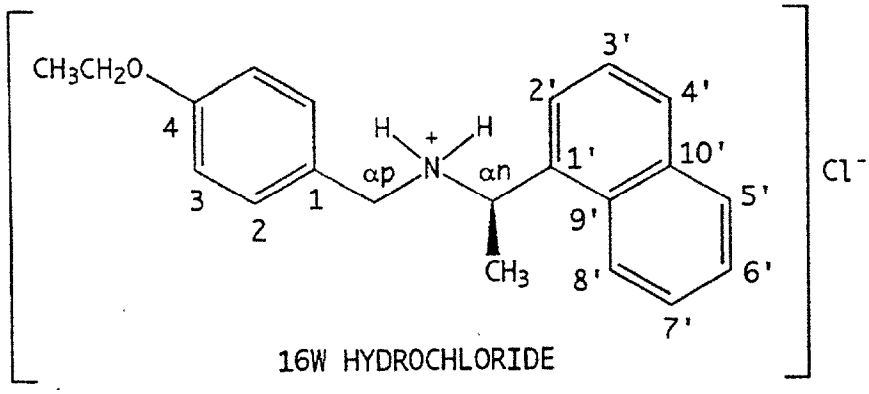
16W HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.35	t	J=6.9	$-OCH_2CH_3$
3H	1.86	d	J=6.8	aliph-CH_3
4H	3.81-3.96	m		$-CH_2$ AND CH_2
1H	5.00	q	J=6.7	aliph-CH-
1H	6.70	d	J=8.4	3
1H	7.19	d	J=8.6	2
2H	7.44-7.54	m	n.a.	
1H	7.58	d	J=8.3	
1H	7.68	dd	$J_1=J_2=7.7$	3'
1H	7.89	d	J=7.7	4' OR 5'
1H	7.91	d	J=7.7	4' OR 5'
1H	8.42	d	J=7.0	2'
1H	10.30	bs	n.a.	aliph-NH_2+
1H	10.72	bs	n.a.	aliph-NH_2+

FIG. 115.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:

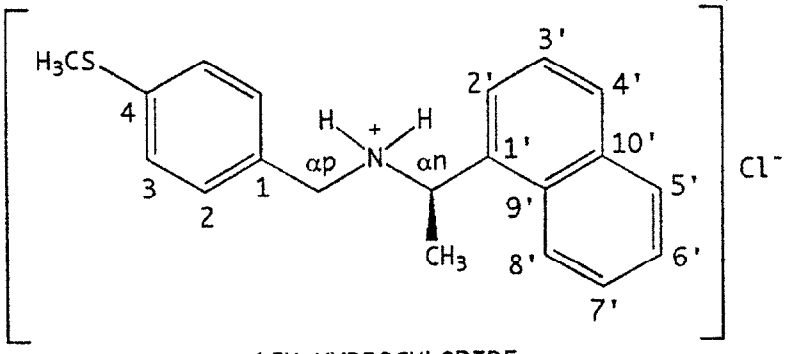


NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
14.51	CH_3	$\underline{C}H_3$-CH_2-O-
21.20	CH_3	aliph-CH_3
47.91	CH_2	-CH_2-
51.27	CH	-CH-
63.16	CH_2	CH_3-$\underline{C}H_2$-O-
114.36	CH	3'
121.43	Q	LEFT SIDE arom-$\underline{C}$-CH_2NH_2
121.52	CH	
---	---	
125.07	CH	
125.93	CH	
125.99	CH	
126.70	CH	
129.08	CH	
---	---	
130.29	Q	
---	---	
132.25	CH	2'
132.33	Q	
133.67	Q	NH_2-CH_2-$\underline{C}$-naphthyl
159.38	Q	arom-$\underline{C}$-OCH_3

FIG. 116.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



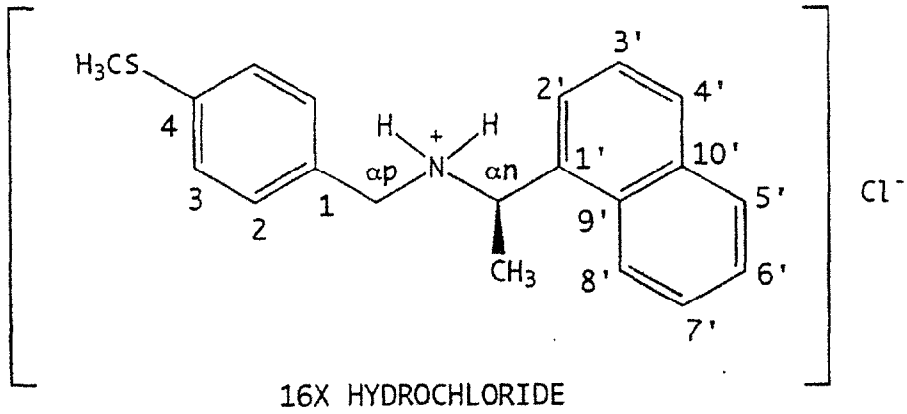
16X HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.87	d	J=6.8	aliph-CH_3
3H	2.38	s	n.a.	-SCH_3
1H	3.82	d	J=13.4	-CH_2-
1H	3.91	d	J=13.2	-CH_2-
1H	5.04	q	J=6.6	aliph-CH-
1H	7.03	d	J=8.2	H-3'
1H	7.20	d	J=8.2	H-2'
2H	7.45-7.55	m	n.a.	
1H	7.59	d	J=7.9	
1H	7.68	dd	J_1=J_2=7.4	3'
1H	7.90	d	J=8.1	4' OR 5'
1H	7.91	d	J=7.0	4' OR 5'
1H	8.39	d	J=7.3	2'
1H	10.38	bs	n.a.	aliph-NH_2+
1H	10.78	bs	n.a.	aliph-NH_2+

FIG. 117.

VARIAN 75 MHz ^{13}C-NMR SPECTRAL ASSIGNMENT OF:



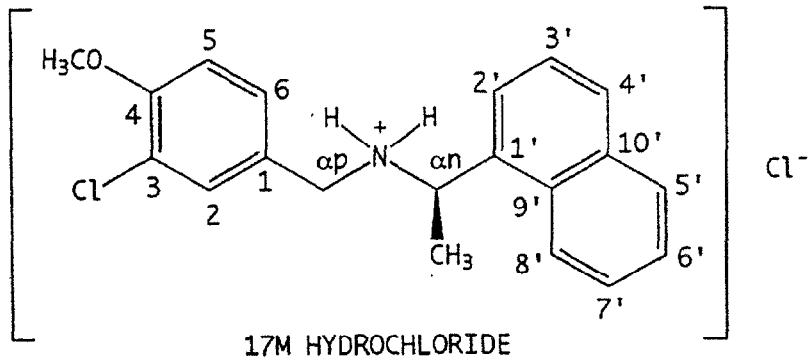
16X HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
14.95	CH_3	S-CH_3
21.18	CH_3	aliph-CH_3
48.02	CH_2	-CH_2-
51.57	CH	-CH-
121.44	CH	
121.10	CH	
---	---	
125.81	CH	
125.95	Q	
125.99	CH	
126.77	CH	
129.12	CH	
129.20	CH	
130.30	Q	
---	---	
131.29	CH	
132.16	CH	2'
133.67	Q	NH_2-CH_2-C-naphthyl
140.18	Q	arom-C-SCH_3

FIG. 118.

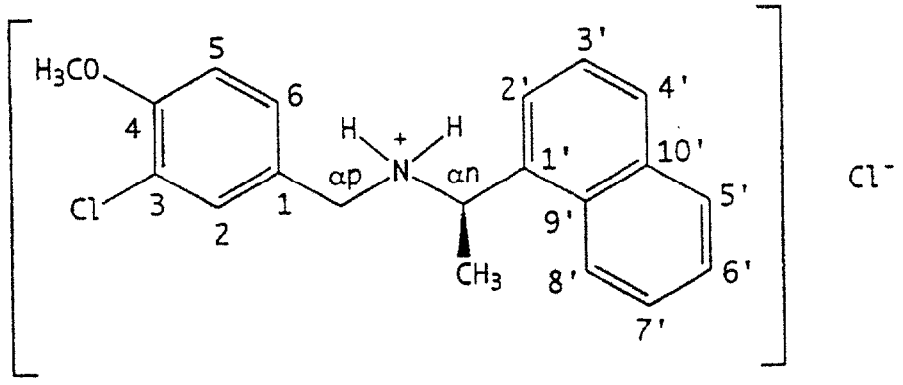
VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.88	d	J=6.6	aliph-CH_3
3H	3.85	s	n.a.	-OCH_3
1H	3.82	d	J=13.1	-CH_2-
1H	3.95	d	J=13.2	-CH_2-
1H	5.03	q	J=7.0	aliph-CH-
1H	6.79 (6.69 calc)	d	J=8.5	5
1H	7.10 (7.13 calc)	s	n.a.	2
1H	7.33 (7.01 calc)	d	J=8.3	6
2H	7.48-7.57	m	n.a.	
1H	7.62	d	J=7.7	
1H	7.69	dd	J=7.4/8.1	3'
1H	7.92	d	J=7.7	4' OR 5'
1H	7.94	d	J=7.7	4' OR 5'
1H	8.38	d	J=7.5	2'
1H	10.42	bs	n.a.	aliph-NH_2+
1H	10.79	bs	n.a.	aliph-NH_2+

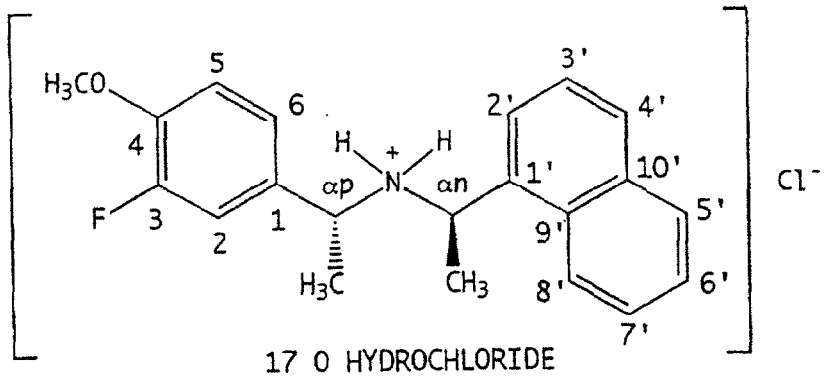
FIG. 119.



21.32	CH_3	aliph-CH_3
47.45	CH_2	-CH_2-
51.47	CH	-CH-
55.96	CH_3	O-CH_3
111.88	CH	5'
121.27	CH	
122.27	Q	
122.65	Q	
125.14	CH	
126.01	CH	
126.14	CH	
127.05	CH	
129.21	CH	
129.35	CH	
130.30	Q	
130.69	CH	
132.09	Q	
132.71	CH	6'
133.76	Q	NH_2-CH_2-C-naphthyl
155.52	Q	arom-C-OCH_3

FIG. 12O.

VARIAN 300 MHz ^{1}H-NMR SPECTRAL ASSIGNMENT OF:



17 O HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.86	d	J=7.0	aliph-CH_3
3H	1.99	d	J=6.8	aliph-CH_3
3H	3.87	s	n.a.	-OCH_3
1H	3.91	q	J=7.0	aliph-CH-
1H	4.80	q	J=6.7	aliph-CH-
1H	6.79	dd	$J_1=J_2=8.5$	
1H	6.89	dd	$J_1=12.0$ $J_2=2.0$	
1H	6.96	d	J=8.7	
1H	7.16	bd	J=7.14	8'
1H	7.34	dd	$J_1=J_2=8.3$	7'
1H	7.49	dd	$J_1=J_2=7.2$	6'
1H	7.71	dd	$J_1=J_2=8.1$	3'
1H	7.90	d	J=8.1	4' OR 5'
1H	7.91	d	J=7.8	4' OR 5'
1H	8.53	bs	n.a.	2'
1H	10.64	bs	n.a.	aliph-NH_2+

FIG. 121.