propyl]-1-(3-methoxyphenyl)ethylamine, 4Z/5A, as an oil; m/z (rel. int.) 283 (M+, 17), 268 (71), 164 (13), 135 (100), 121 (21), 105 (27), 91 (26), 77 (14).

Preparation of 4Y

In a similar fashion, 2-chloroacetophenone was used to prepare 3-methyl-3-(2-chlorophenyl)cinnamonitrile. The nitrile was catalytically reduced (palladium hydroxide, acetic acid, 60 p.s.i. hydrogen 2 hr) to generate 3-methyl-3-(2-chlorophenyl)propylamine. An equal molar amount of the amine, 3'-methoxyacetophenone and 1.25 molar equivalents titanium (IV) isopropoxide were mixed 4 hr at rt and the intermediate imine treated with an ethanolic sodium cyanoborohydride (5 ml of 1 M, 5 mmol). Work-up and chromatography afforded N-[3-methyl-3-(2-chlorophenyl)propyl]-1-(3-methoxyphenyl)ethylamine, 4Y, as an oil; m/z (rel. int.) 283 (M+, 17) 268 (71), 164 (13), 135 (100), 121 (21), 105 (27), 91 (26), 77 (14).

Preparation of 6T

A solution of NPS *R*-568 (30.3 g 100 mmol) in dichloromethane at -78°C was treated dropwise with boron-tribromide (50 g, 200 mmol). The reaction was stirred 1 hr at rt and poured over ice. The hydrobromide was extracted from the aqueous phase with chloroform. The chloroform solubles were then washed (4 x 100 ml) with 50% HCl. The chloroform wash was dried over anhydrous magnesium sulfate and concentrated to afford (*R*)-N-[3-(2-chlorophenyl)propyl]-1-(3-hydroxyphenyl)ethylamine hydrochloride as a solid. A solution of sodium hydride (0.48 g, 20 mmol) in dimethylformamide was treated with (*R*)-N-[3-(2-chlorophenyl)propyl]-1-(3-hydroxyphenyl)ethylamine hydrochloride (3.25 g, 10 mmol) and the reaction stirred 1 hr at rt. The reaction was treated with iodoethane (1.71 g, 11 mmol) and stirred 16 hr at rt. Work-up and chromatography through silica using 3% methanol in chloroform afforded (*R*)-N-[3-(2-chlorophenyl)propyl]-1-(3-

ethoxyphenyl)ethylamine, 6T, as an oil; m/z (rel. int.) 316 (M+,1), 302 (100), 282 (11), 196 (5), 178 (7), 149 (74), 121 (34), 103 (25), 91 (28), 77 (29).

Preparation of 6R

NPS *R*-467 was used in a similar fashion to prepare (*R*)-N-(3-phenylpropyl)-1-(3-ethoxyphenyl)ethylamine, 6R, as an oil; m/z (rel. int.) 283 (M+,10), 268 (74), 178 (11), 162 (8), 149 (100), 121 (30), 103 (16), 91 (86), 77 (29).

Preparation of 3U

An equal molar mixture of 3,3-diphenylpropylamine (2.11 g, 10 mmol), 1'-acetonaphthone (1.70 g, 10 mmol) and 1.25 equivalents of titanium (IV) isopropoxide (3.55 g, 12.5 mmol) were stirred 4 hr at rt. The reaction mixture was then treated with a 1 M solution of ethanolic sodium cyanoborohydride (12.5 ml, 12.5 mmol) and stirred 16 hr at rt. The reaction was diluted with diethyl ether (50 ml) and treated with water (0.72 ml, 40 mmol). After mixing thoroughly the mixture was centrifuged and the ether layer decanted and concentrated to a milky oil. The oil was suspended in diethyl ether and filtered through a 0.45 μM CR PTFE Acrodisc. The diethyl ether filtrate was concentrated to afford *N*-(3,3-diphenylpropyl)-1-(1-naphthyl) ethylamine, 3U, as a clear, colorless oil; m/z (rel. int.) 365 (M+, 17), 350 (19), 181 (23), 155 (100), 141 (25), 115 (11), 91 (13), 77 (6).

Preparation of 6F

In a similar fashion equal molar amounts 1-(3-methoxyphenyl)ethylamine (1.51 g, 10 mmol), 2'-acetonaphthone (1.70 g, 10 mmol) and 1.25 equivalents of titanium (IV) isopropoxide (3.55 g, 12.5 mmol) were treated as above. Work-up yielded *N*-[1-(2-naphthyl)ethyl]-1-(3-methoxyphenyl)ethylamine, 6F, as a clear, colorless oil;

m/z (rel. int.) 305 (M+,1), 290 (35), 170 (49), 155 (100), 135 (55), 115 (8), 105 (10), 91 (9), 77 (10).

Preparation of 4G

In a similar fashion equal molar amounts of (*R*))-1-phenylethylamine,, 1'-acetonaphthone and 1.25 equivalents of titanium (IV) isopropoxide were mixed and the resulting intermediate imine was reduced with ethanolic sodium cyanoborohydride. Work-up and chromatography yielded *N*-[1-(1-naphthyl)ethyl)-1-phenylethylamine, 4G, as a clear, colorless oil; m/z (rel. int.) 275 (M+,16), 260 (79), 155 (100), 127 (27), 105 (70), 77 (32).

Preparation of 4H

In a similar fashion equal molar amounts of (*R*)-1-phenylethylamine, 2'-acetonaphthone and 1.25 equivalents of titanium (IV) isopropoxide were mixed and the resulting intermediate imine was reduced with ethanolic sodium cyanoborohydride. Work-up and chromatography yielded *N*-[1-(2-naphthyl)ethyl]-1-phenylethylamine, 4H, as a clear, colorless oil; m/z (rel. int.) 275 (M+,1), 260 (61), 155 (100), 120 (36), 105 (55), 77 (15).

Preparation of 6E

In a similar fashion equal molar amounts of 1-(3-methoxyphenyl)ethylamine, 1'-acetonaphthone and 1.25 equivalents of titanium (IV) isopropoxide were mixed and the resulting intermediate imine was reduced with ethanolic sodium cyanoborohydride. Work-up and chromatography yielded *N*-1-(1-naphthyl)ethyl-1-(3-methoxyphenyl)ethylamine, 6E, as a clear, colorless oil; m/z (rel. int.) 305 (M+,10), 290 (30), 170 (43), 155 (100), 135 (69), 115 (9), 105 (15), 91 (14), 77 (18).

Example 19: Pharmaceutical Formulation

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

TABLE 3

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

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

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

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

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

Other embodiments are within the following claims. Thus, while several embodiments have been shown and described, various modifications may be made, without departing from the spirit and scope of the present invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: NPS Pharmaceuticals, Inc.

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

(iii) NUMBER OF SEQUENCES: 2

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

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

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

Prior applications total, including application described below: 2

(A) APPLICATION NUMBER: U.S. 08/353,784
(B) FILING DATE: 8 December, 1994

(A) APPLICATION NUMBER: PCT/US/94/12117
(B) FILING DATE: 21 October, 1994

(viii) ATTORNEY/AGENT INFORMATION:

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

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(C) TELEX: 67-3510

(2) INFORMATION FOR SEQ ID NO: 1:

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

(ii) MOLECULE TYPE: cDNA to mRNA

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

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

GCTGCTGTGG CCGGACCCGA AGGCGGGCGC CGGGAGCGCA 40

GCGAGCCAGA CGCGCCTCTC CAAGACCGTG ACCTTGGCAT 80

AGGGAGCGGG GCTGCGCGCA GTCCTGAGAT CAGACCAGAG 120

CTCATCCTCG TGGAGACCCA CGGCCGAGGG GCCGGAGCTG 160

CCTCTGTGCG AGGGAGCCCT GGCCGCGGCG CAGAAGGCAT 200

CACAGGAGGC CTCTGCATGA TGTGGCTTCC AAAGACTCAA 240

GGACCACCCA CATTACAAGT CTGGATTGAG GAAGGCAGAA 280

ATGGAGATTC AAACACCACG TCTTCTATTA TTTTATTAAT 320

CAATCTGTAG ACATGTGTCC CCACTGCAGG GAGTGAACTG 360

CTCCAAGGGA GAAACTTCTG GGAGCCTCCA AACTCCTAGC 400

TGTCTCATCC CTTGCCCTGG AGAGACGGCA GAACC 435

ATG GCA TTT TAT AGC TGC TGC TGG GTC CTC TTG GCA 471
Met Ala Phe Tyr Ser Cys Cys Trp Val Leu Leu Ala
1 5 10

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CTC ACC TGG CAC ACC TCT GCC TAC GGG CCA GAC CAG        507
Leu Thr Trp His Thr Ser Ala Tyr Gly Pro Asp Gln
          15                  20

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

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

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

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

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

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

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

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

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

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

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

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

TCC TCC AGC AGA CTC CTC AGC AAC AAG AAT CAA TTC        975
Ser Ser Ser Arg Leu Leu Ser Asn Lys Asn Gln Phe
    170                 175                 180
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AAG TCT TTC CTC CGA ACC ATC CCC AAT GAT GAG CAC      1011
Lys Ser Phe Leu Arg Thr Ile Pro Asn Asp Glu His
                185                 190

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

GGAGAAGACT GGGCTAGGGA GAATGCAGAG AGGTTTCTTG          3749

GGGTCCCAGG GATGAGGAAT CGCCCCAGAC TCCTTTCCTC          3789

TGAGGAAGAA GGGATAATAG ACACATCAAA TGCCCCGAAT          3829

TTAGTCACAC CATCTTAAAT GACAGTGAAT TGACCCATGT          3869

TCCCTTTAAA ATTAAAAAAA AGAAGAGCCT TGTGTTTCTG          3909

TGGTTGCATT TGTCAAAGCA TTGAGATCTC CACGGTCAGA          3949

TTTGCTGTTC ACCCACATCT AATGTCTCTT CCTCTGTTCT          3989

ATCCCACCCA ACAGCTCAGA GATGAAACTA TGGCTTTAAA          4029

CTACCCTCCA GAGTGTGCAG ACTGATGGGA CATCAAATTT          4069

GCCACCACTA GAGCTGAGAG TCTGAAAGAC AGAATGTCAC          4109

CAGTCCTGCC CAATGCCTTG ACAACAGACT GAATTTTAAA          4149

TGTTCACAAC ATAAGGAGAA TGTATCTCCT CCTATTTATG          4189

AAAACCATAT GATATTTTGT CTCCTACCTG CTGCTGCTAT          4229

TATGTAACAT CCAGAAGGTT TGCACCCCTC CTATACCATA          4269

TGTCTGGTTC TGTCCAGGAC ATGATACTGA TGCCATGTTT          4309

AGATTCCAGG ATCACAAGAA TCACCTCAAA TTGTTAGGAA          4349
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GGGACTGCAT AAACCAATGA GCTGTATCTG TAATTAATAT 4389

TCCTATATGT AGCTTTATCC TTAGGAAAAT GCTTCTGTTG 4429

TAATAGTCCA TGGACAATAT AAACTGAAAA ATGTCAGTCT 4469

GGTTTATATA AGGCAGTATT ATTGAGCTCT ATTTCCCCAC 4509

CCCACTATCC TCACTCCCAT AAGCTAAGCC TTATGTGAGC 4549

CCCTTCAGGG ACTCAAGGGT CCAGAAGTCC CTCCCATCTC 4589

TACCCCAAAG AATTCCTGAA GCCAGATCCA CCCTATCCCT 4629

GTACAGAGTA AGTTCTCAAT TATTGGCCTG CTAATAGCTG 4669

CTAGGGTAGG AAAGCGTGGT TCCAAGAAAG ATCCACCCTC 4709

AAATGTCGGA GCTATGTTCC CTCCAGCAGT GGTATTAATA 4749

CTGCCGGTCA CCCAGGCTCT GGAGCCAGAG AGACAGACCG 4789

GGGTTCAAGC CATGGCTTCG TCATTTGCAA GCTGAGTGAC 4829

TGTAGGCAGG GAACCTTAAC CTCTCTAAGC CACAGCTTCT 4869

TCATCTTTAA AATAAGGATA ATAATCATTC CTTCCCCTCA 4909

GAGCTCTTAT GTGGATTAAA CGAGATAATG TATATAAAGT 4949

ACTTTAGCCT GGTACCTAGC ACACAATAAG CATTCAATAA 4989

ATATTAGTTA ATATTAT 5006

(2) INFORMATION FOR SEQ ID NO: 2:

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

(ii) MOLECULE TYPE: cDNA to mRNA

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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GGCTTCCAAA GACTCAAGGA CCACCCACAT TACAAGTCTG               200

GATTGAGGAA GGCAGAAATG GAGATTCAAA CACCACGTCT               240

TCTATTATTT TATTAATCAA TCTGTAGACA TGTGTCCCCA               280

CTGCAGGGAG TGAACTGCTC CAAGGGAGAA ACTTCTGGGA               320

GCCTCCAAAC TCCTAGCTGT CTCATCCCTT GCCCTGGAGA               360

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CAG CAG CCC CTG ACC CTC CCA CAG CAG CAA CGA TCT      3240
Gln Gln Pro Leu Thr Leu Pro Gln Gln Gln Arg Ser
945                 950                 955
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100

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CAG CAG CAG CCC AGA TGC AAG CAG AAG GTC ATC TTT      3276
Gln Gln Gln Pro Arg Cys Lys Gln Lys Val Ile Phe
            960                 965

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

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

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

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

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

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

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

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

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

AAT TCA TAAAATGGAA GGAGAAGACT GGGCTAGGGA             3636
Asn Ser

GAATGCAGAG AGGTTTCTTG GGGTCCCAGG GATGAGGAAT          3676

CGCCCCAGAC TCCTTTCCTC TGAGGAAGAA GGGATAATAG          3716

ACACATCAAA TGCCCCGAAT TTAGTCACAC CATCTTAAAT          3756

GACAGTGAAT TGACCCATGT TCCCTTTAAA AAAAAAAAAA          3796

AAAAAGCGGC CGC                                      3809
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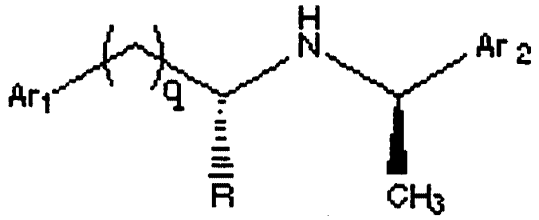
Claims

1. An inorganic ion receptor modulating compound having the formula:



wherein Ar_1 is either naphthyl or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, lower alkoxy, lower thioalkyl, methylene dioxy, lower haloalkyl, lower haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, $N(CH_3)_2$, phenyl, phenoxy, benzyl, benzyloxy, α,α-dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, acetyl, ethylene dioxy;

Ar_2 is either naphthyl or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, lower alkoxy, lower thioalkyl, methylene dioxy, lower haloalkyl, lower haloalkoxy, OH, CH_2OH, $CONH_2$, CN, and acetoxy;

q is 0, 1, 2, or 3; and

R is either H, lower alkyl;

and pharmaceutically salts and complexes thereof;

wherein said compound modulates one or more inorganic ion receptor activities.

2. The compound of claim 1, said Ar_1 phenyl, if present, has 1 to 5 substituents each independently selected from the group consisting of, isopropyl, CH_3O, CF_3 CH_3S, CF_3O, I, Cl, F, and CH_3;

said Ar_2 phenyl, if present, has 1 to 5 substituents each independently selected from the group consisting of, isopropyl, CH_3O, CH_3S, CF_3O, I, Cl, F, CF_3, and CH_3;

said compound is a calcimimetic; and

said inorganic ion receptor activity is calcium receptor activity.

3. The compound of claim 2, wherein q is 2, said Ar_1 phenyl having 1 to 5 substituents is present, and said Ar_2 phenyl having 1 to 5 substituents is present.

4. Compound of claim 3, said Ar_2 phenyl is a *meta*-methoxy phenyl.

5. The compound of claim 2, wherein q is 0 and said Ar_2 naphthyl is present.

6. The compound of claim 5, wherein said Ar_1 phenyl having 1 to 5 substituents is present.

7. The compound of claim 2, wherein q is 2, said Ar_1 phenyl having 1 to 5 substituents is present, and said Ar_2 naphthyl.

8. The compound of claim 2, wherein said Ar_1 phenyl, if present, has 1 to 5 substituents each independently selected from the group consisting of, CF_3O, I, Cl, F, and CF_3; and

said Ar_2 phenyl, if present, has 1 to 5 substituents each independently selected from the group consisting of, CF_3O, I, Cl, F, CH_3O, and CF_3.

9. The compound of claim 3, wherein said Ar_1 phenyl has 1 to 5 substituents each independently selected from the group consisting of, CF_3O, I, Cl, F, and CF_3; and

said Ar_2 phenyl has 1 to 5 substituents each independently selected from the group consisting of, CF_3O, I, Cl, F, CH_3O, and CF_3.

10. The compound of claim 9, wherein said Ar_2 phenyl is a *meta*-methoxy phenyl.

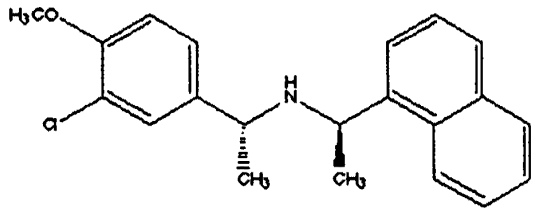
11. The compound of claim 2, wherein R is CH_3.

12. The compound of claim 3, wherein R is CH_3.

13. The compound of claim 4, wherein R is CH_3.

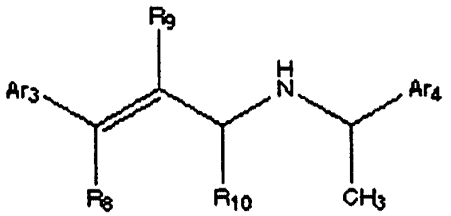
14. The compound of claim 7, wherein R is CH_3

15. The compound of claim 11, wherein said compound has the formula:



or pharmaceutically acceptable salts and complexes thereof.

16. An inorganic ion receptor modulating compound having the formula:



wherein Ar_3 is either naphthyl or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, lower alkoxy, lower thioalkyl, methylene dioxy, lower haloalkyl, lower haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, benzyl, benzyloxy, dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(CH_3)_2$, acetyl, ethylene dioxy;

Ar_4 is either naphthyl or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, lower alkoxy, lower thioalkyl, methylene dioxy, lower haloalkyl, lower haloalkoxy, OH, CH_2OH, $CONH_2$, CN, and acetoxy;

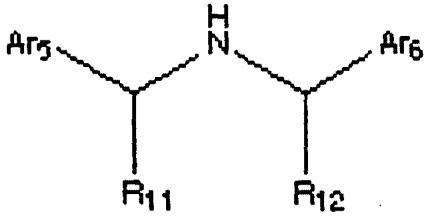
R_8 is either hydrogen or phenyl;

R_9 is either hydrogen or methyl; and

R_{10} is either hydrogen, methyl, or phenyl;

or pharmaceutically acceptable salts and complexes thereof.

17. An inorganic ion receptor modulating compound having the formula:



wherein Ar_5 is either naphthyl or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, lower alkoxy, lower thioalkyl, methylene dioxy, lower haloalkyl, lower haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, benzyl, benzyloxy, α,α-dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, acetyl, ethylene dioxy, -CH=CH-phenyl;

Ar_6 is either naphthyl or phenyl optionally substituted with 0 to 5 substituents each independently

selected from the group consisting of, acetyl, lower alkyl, halogen, lower alkoxy, lower thioalkyl, methylene dioxy, lower haloalkyl, lower haloalkoxy, OH, CH_2OH, $CONH_2$, CN, carbomethoxy, $OCH_2C(O)C_2H_5$ and acetoxy;

R_{11} is hydrogen or methyl; and

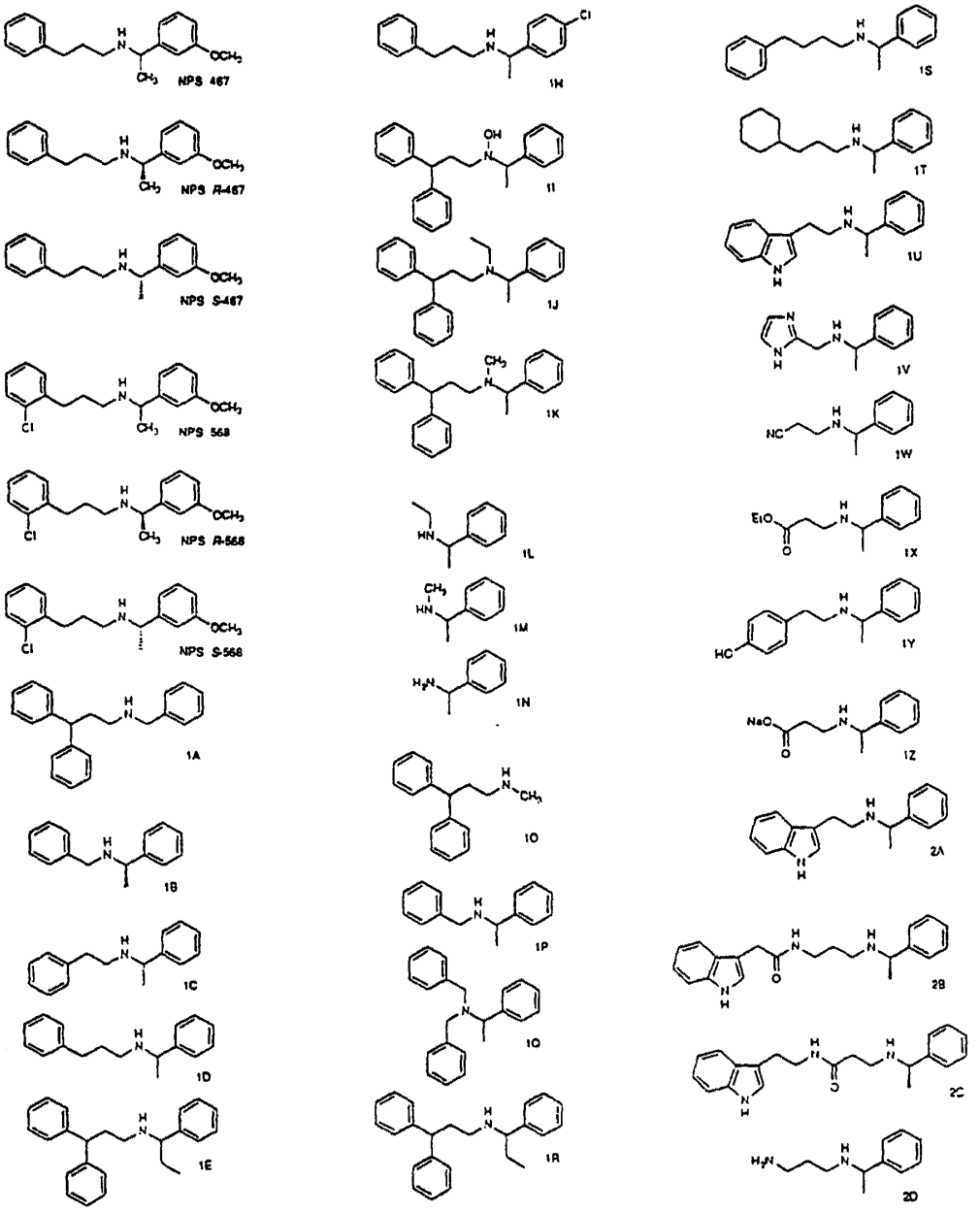
R_{12} is hydrogen or methyl.

18. A pharmaceutical composition comprising a compound of any of claims 1-17 and a pharmaceutical acceptable carrier.

19. A method for treating a patient in need of such treatment comprising the step of administering to said patient a therapeutically effective amount of the pharmaceutical composition of claim 18.

20. The method of claim 19, wherein said patient is a human, said disease is characterized by either, or both, of: (1) abnormal calcium homeostasis, and (2) an abnormal amount of an extracellular or intracellular messenger whose production can be affected by calcium receptor activity; and said compound is a calcimimetic.

21. The method of claim 19, wherein said patient is a human and said disease selected from the group consisting of primary and secondary hyperparathyroidism, Paget's disease, hypercalcemia malignancy, osteoporosis, hypertension, and renal osteodystrophy.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1C
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1N
1O
1P
1Q
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2A
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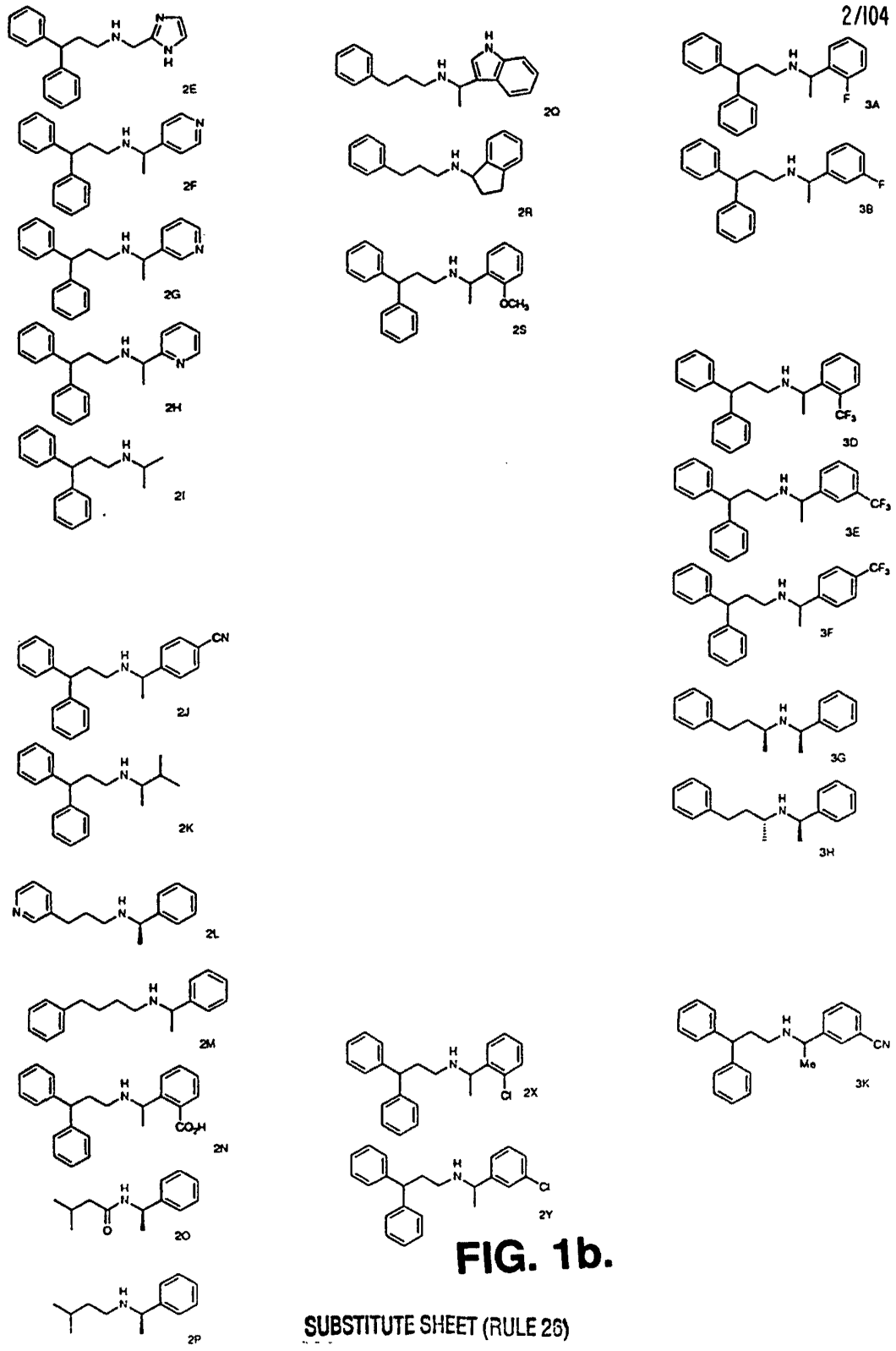
2C
2D

FIG. 1a.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2N
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2P
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2R
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2Y
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3B
3D
3E
3F
3G
3H
3K

FIG. 1b.

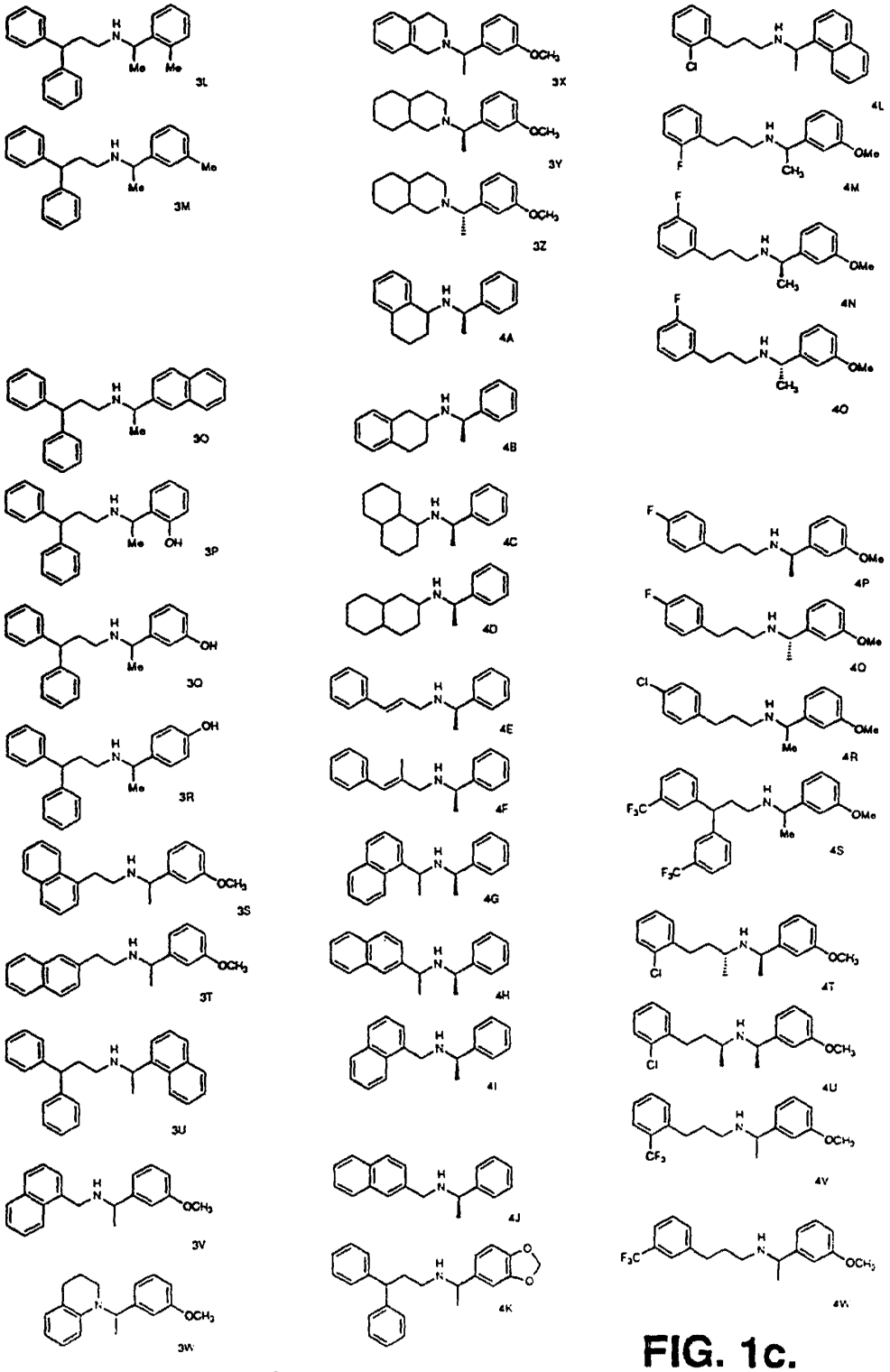
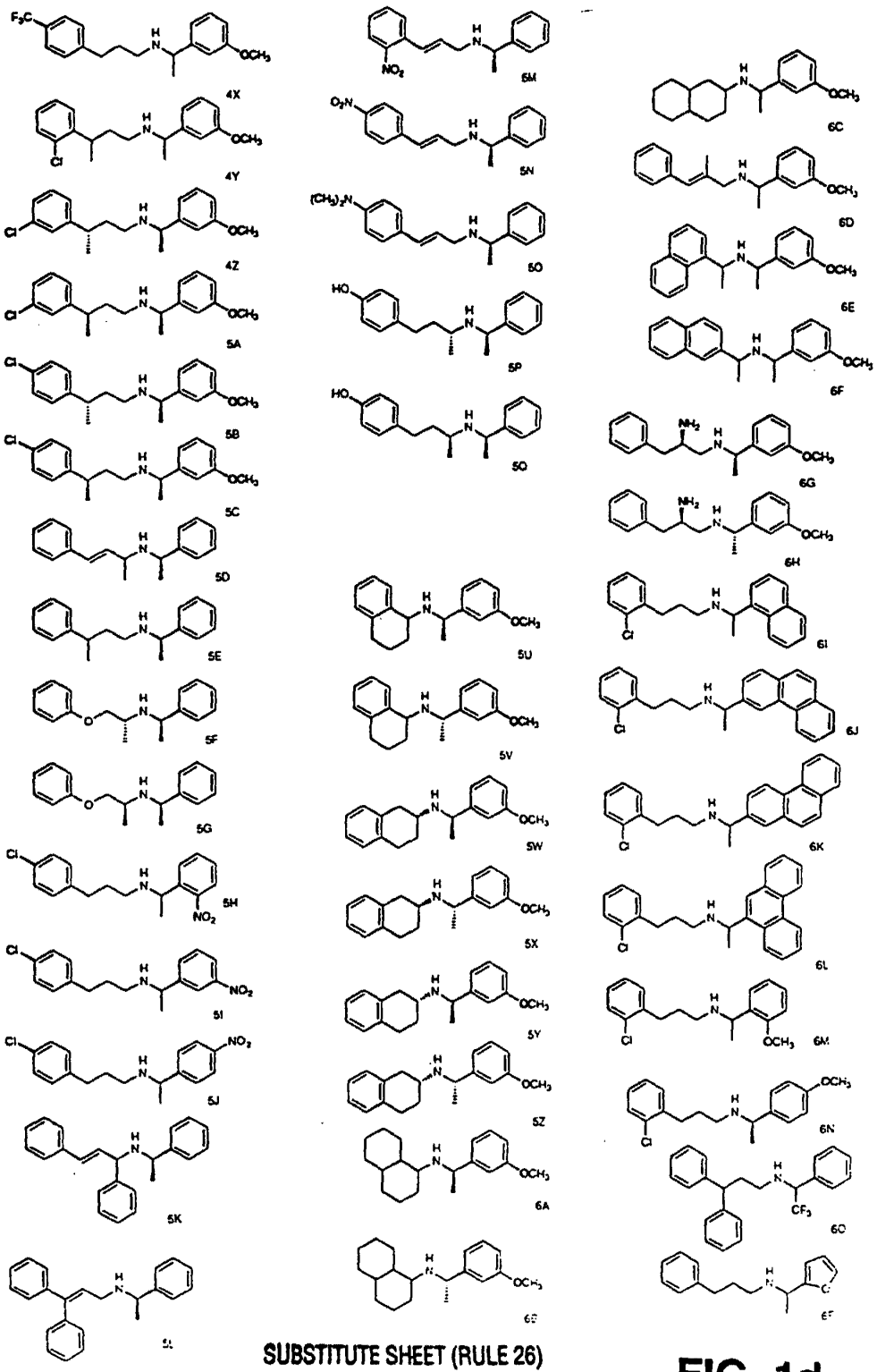


FIG. 1c.



SUBSTITUTE SHEET (RULE 26)

FIG. 1d.

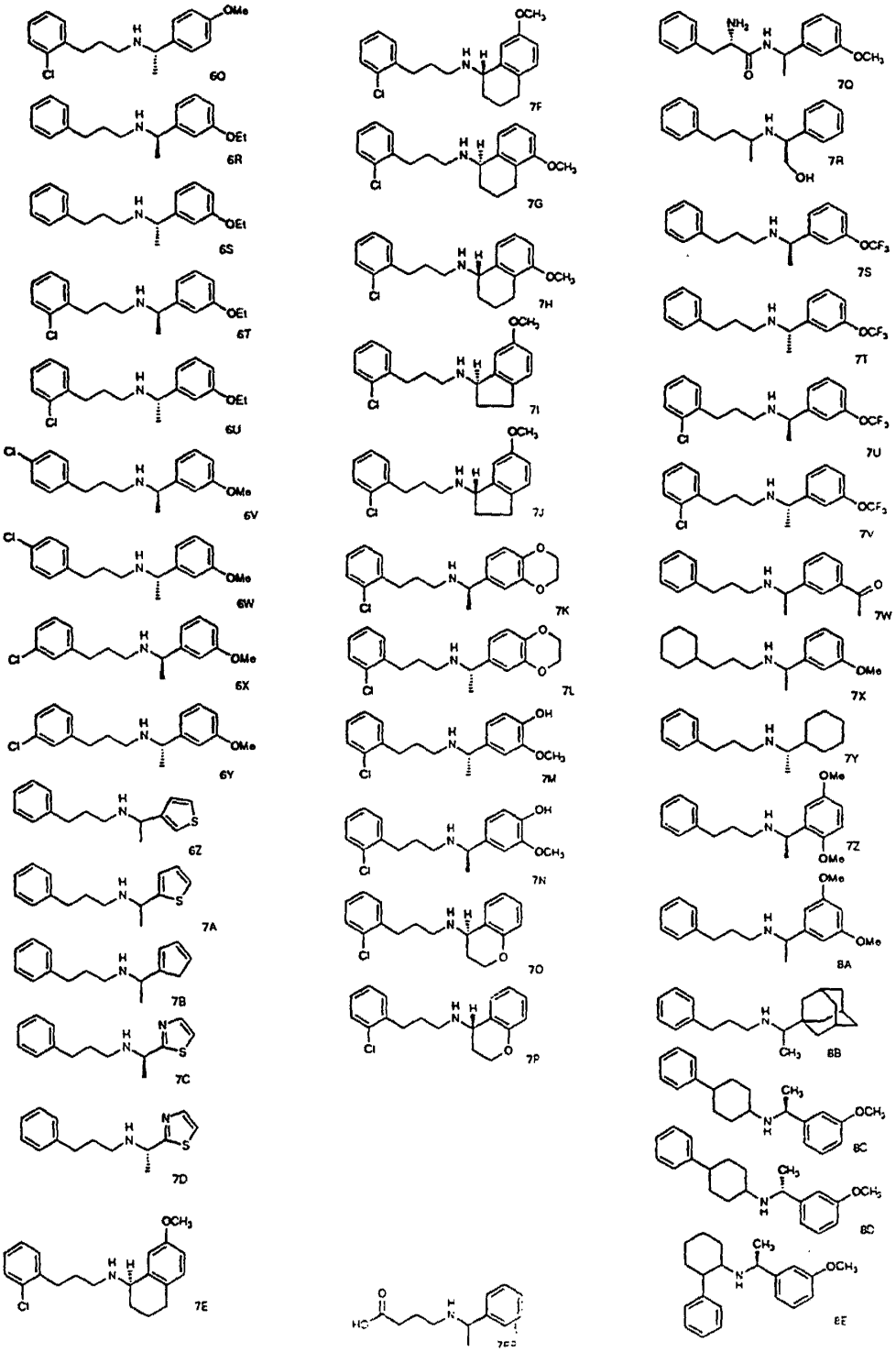

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FIG. 1e.

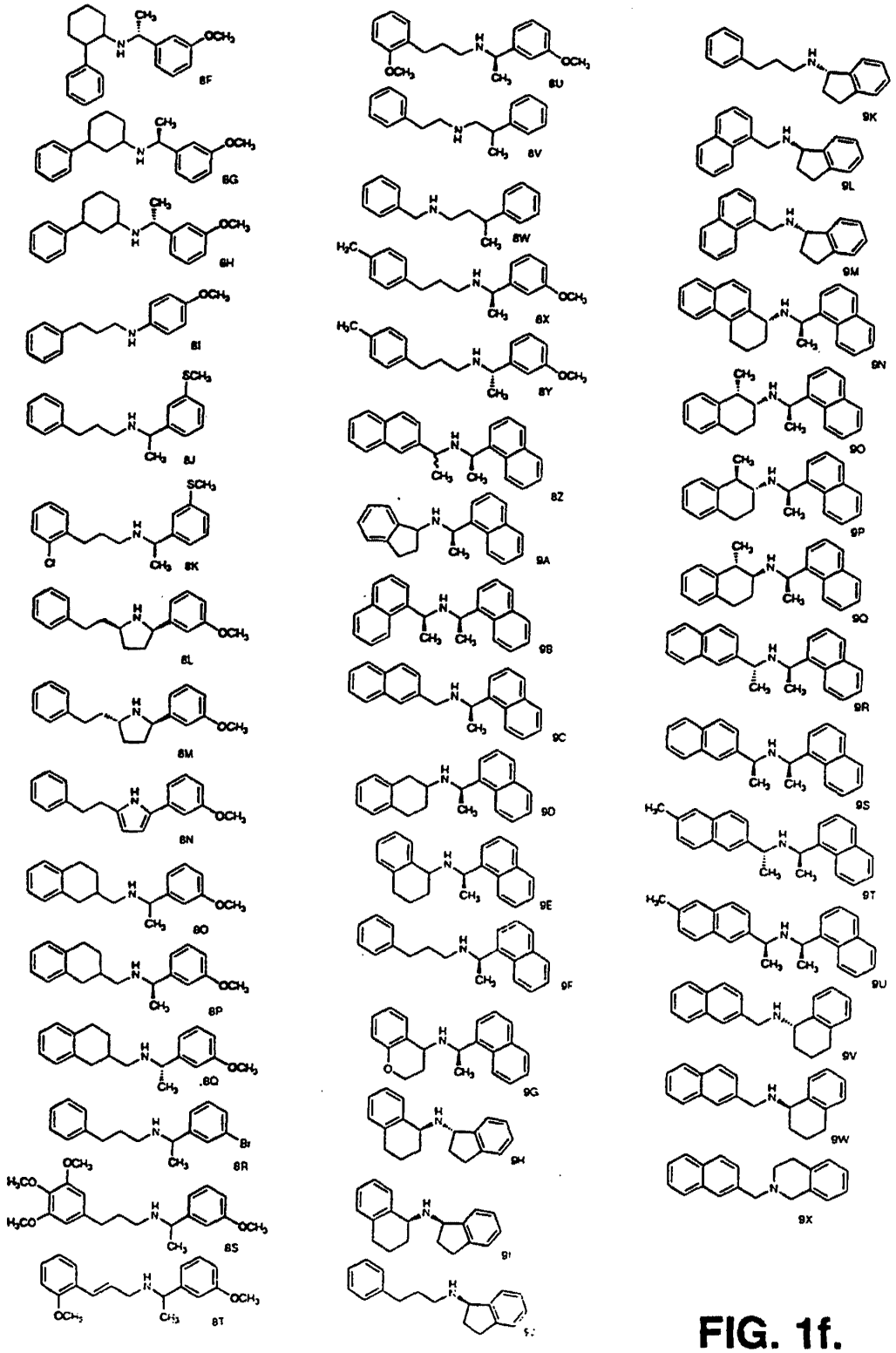
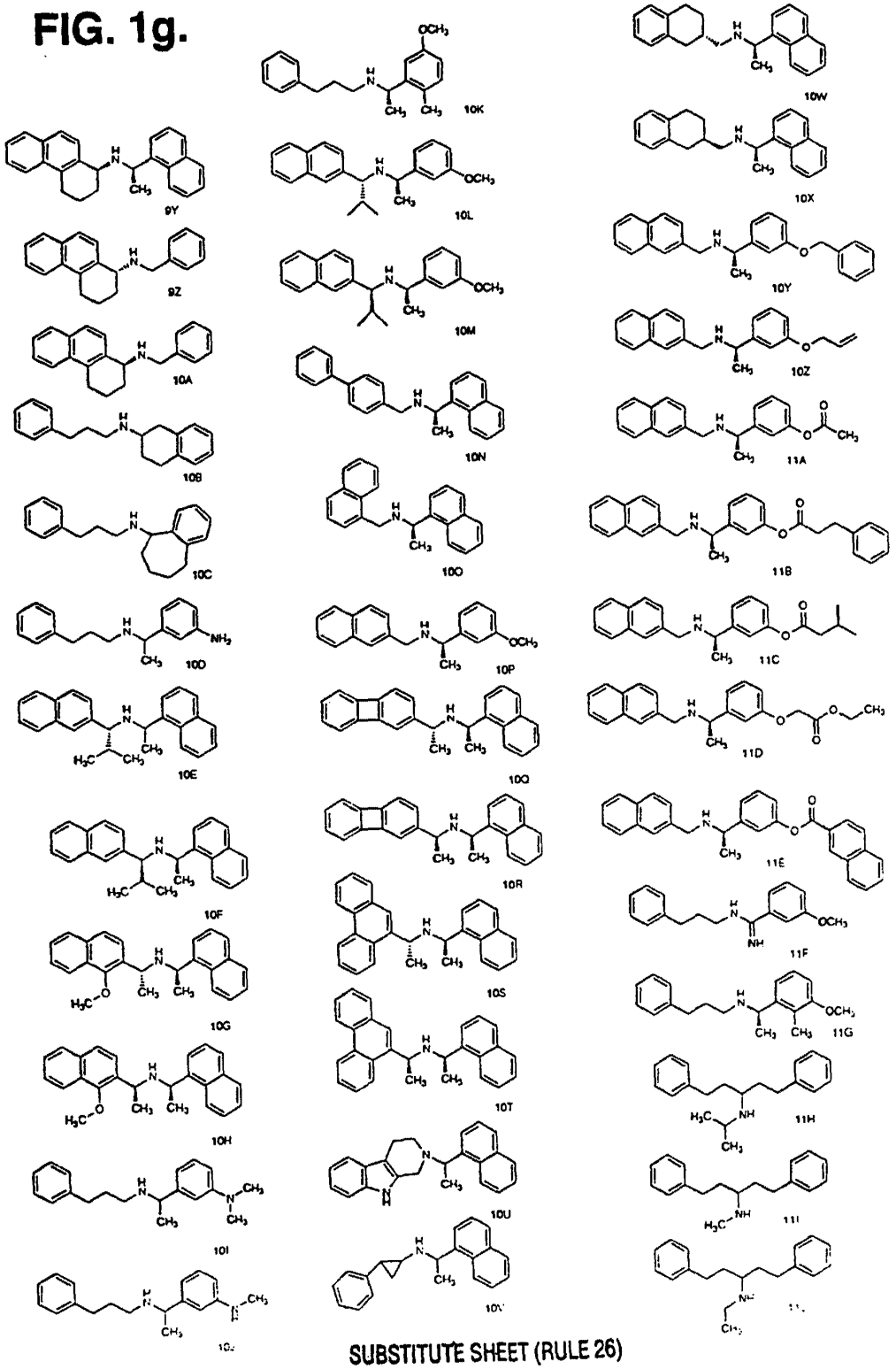


FIG. 1f.

FIG. 1g.



SUBSTITUTE SHEET (RULE 26)

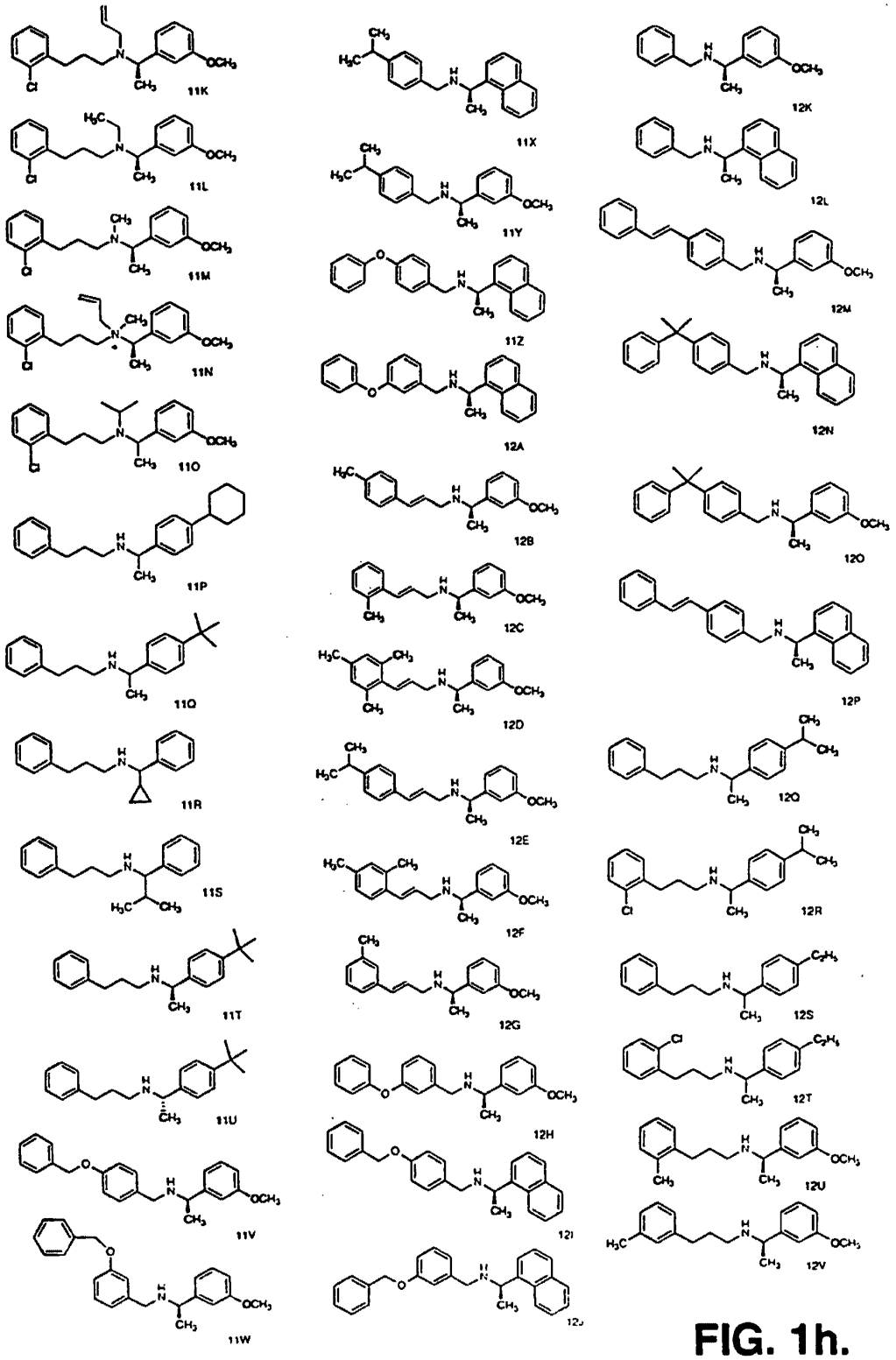

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FIG. 1h.

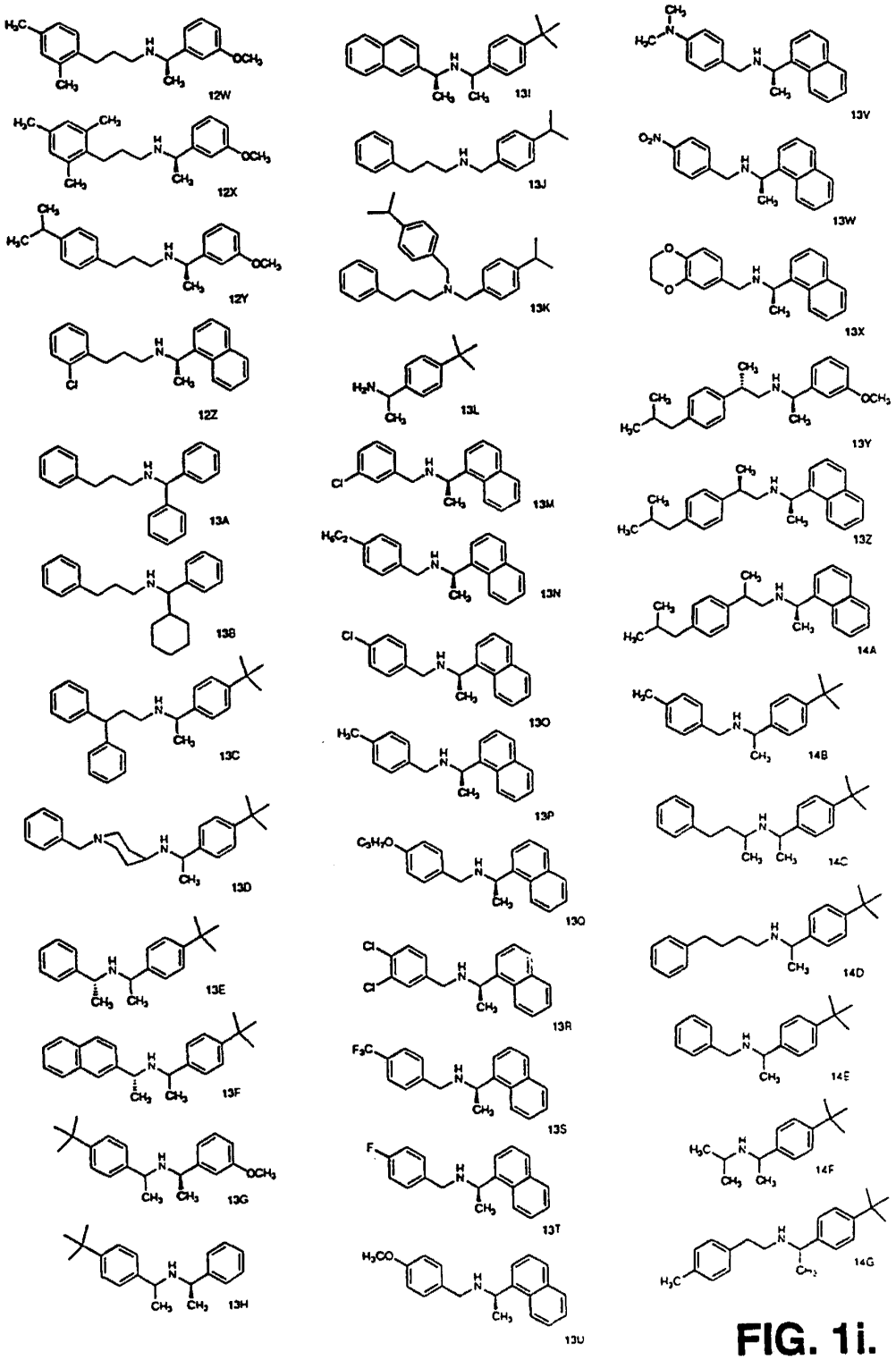
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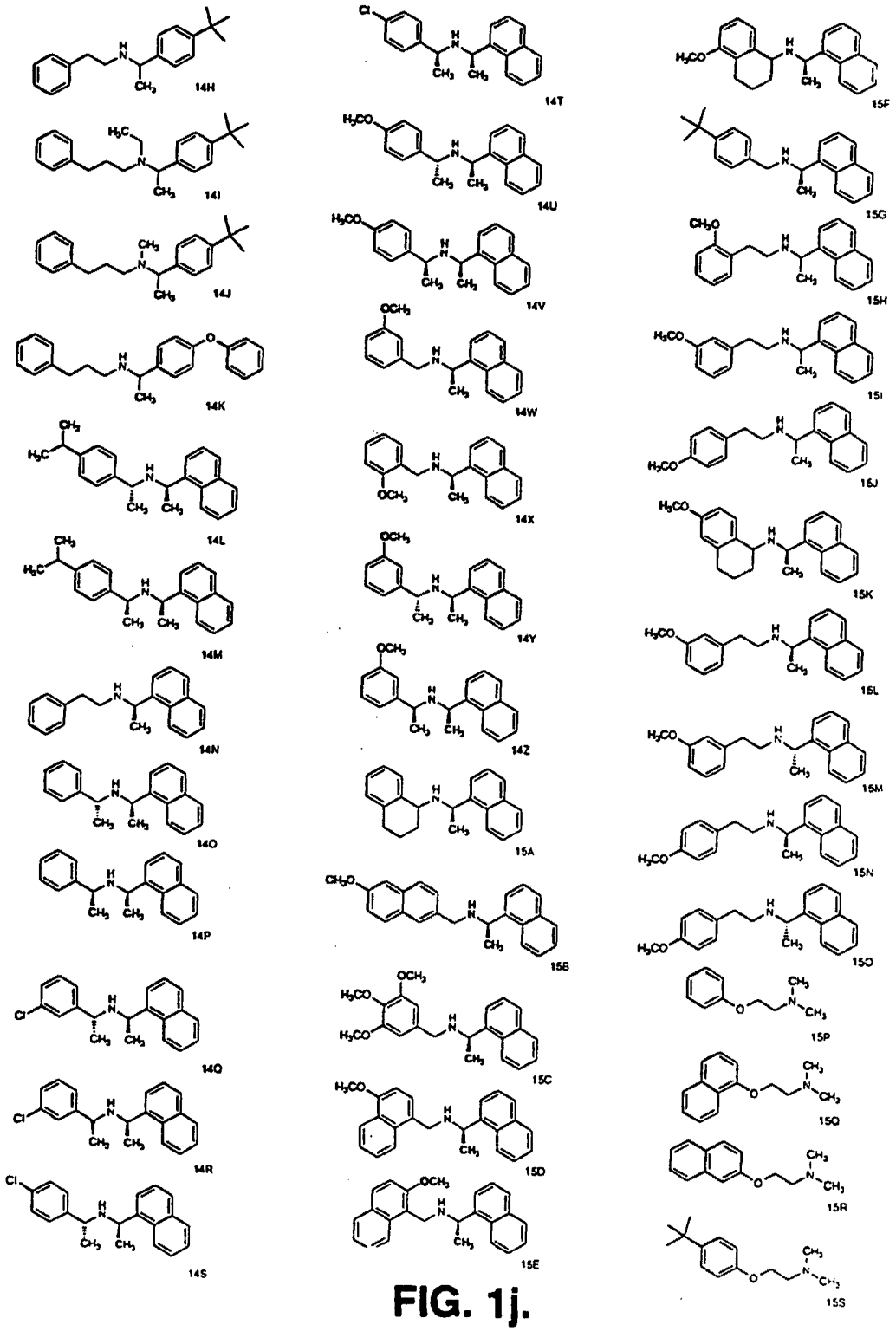
FIG. 1i.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15S

FIG. 1j.

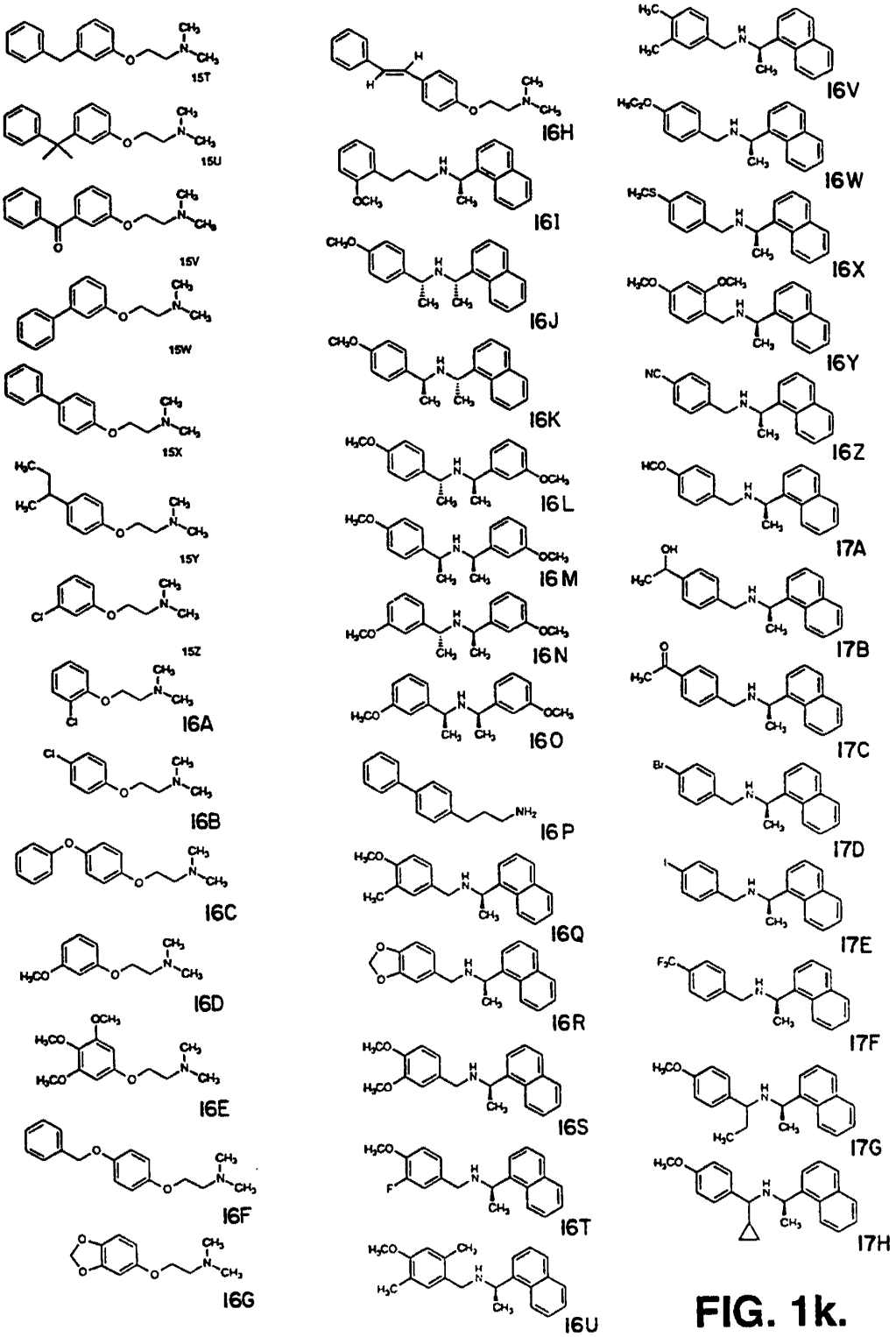
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FIG. 1k.

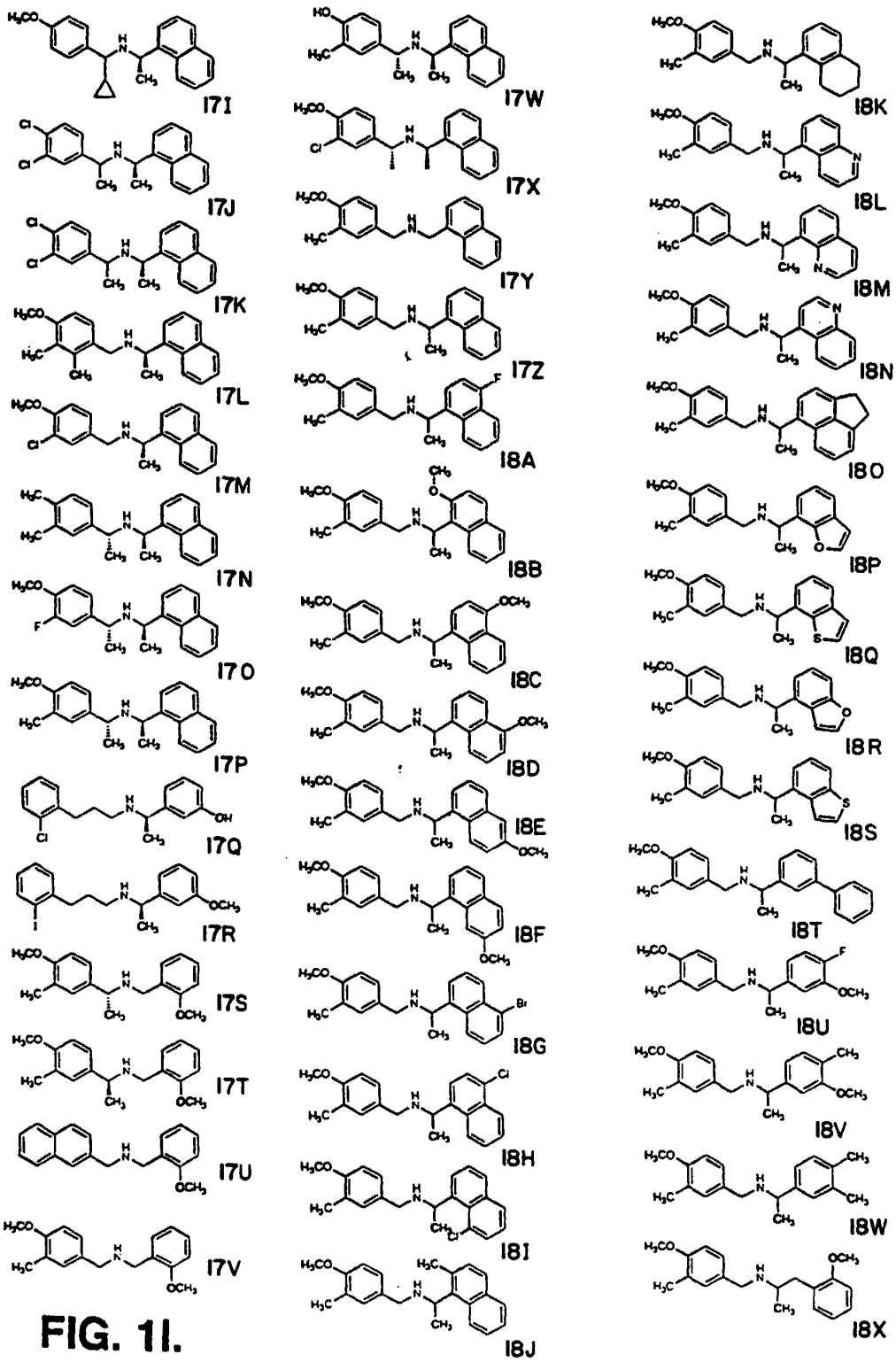
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FIG. 1I.

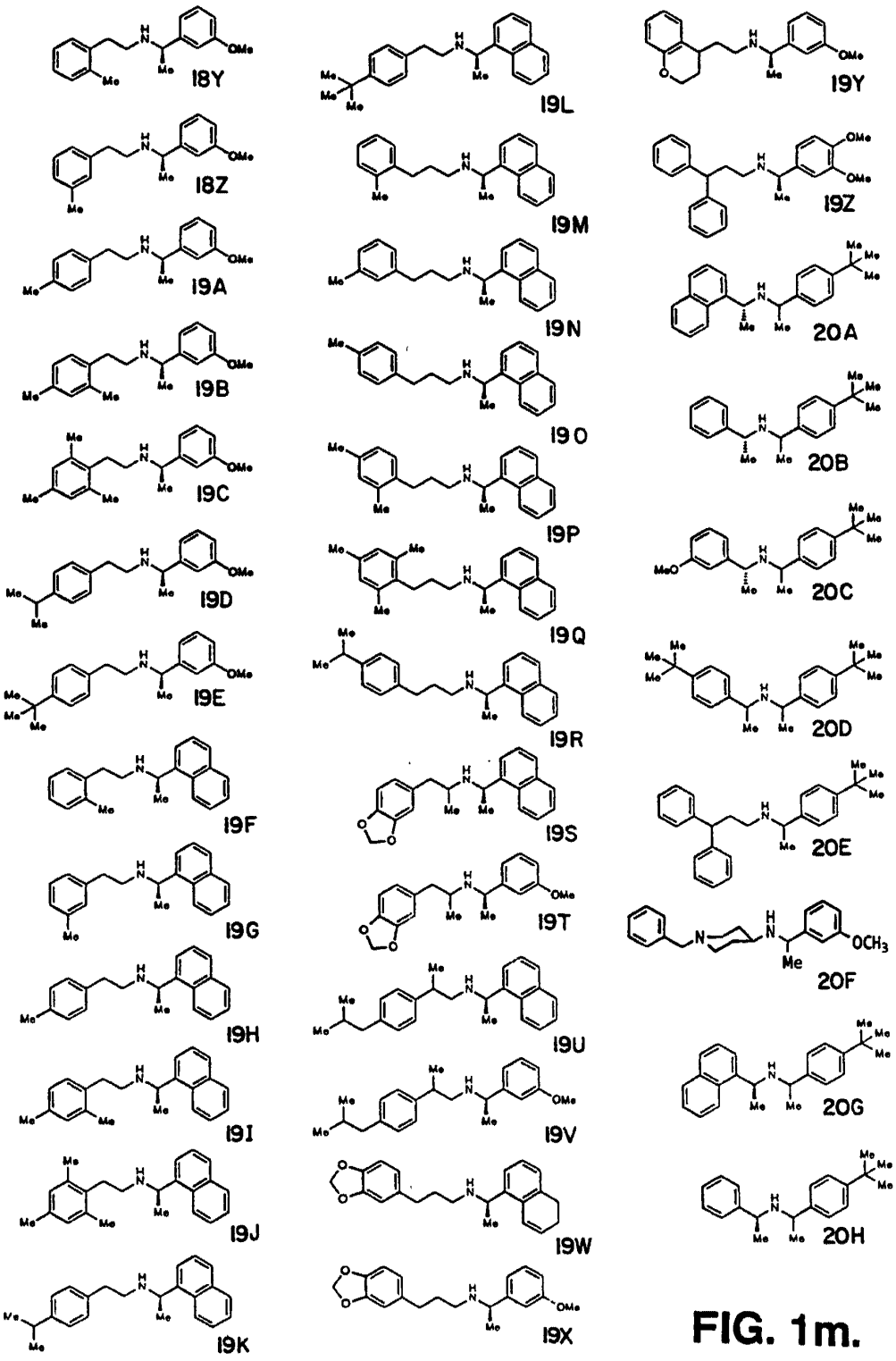


FIG. 1m.

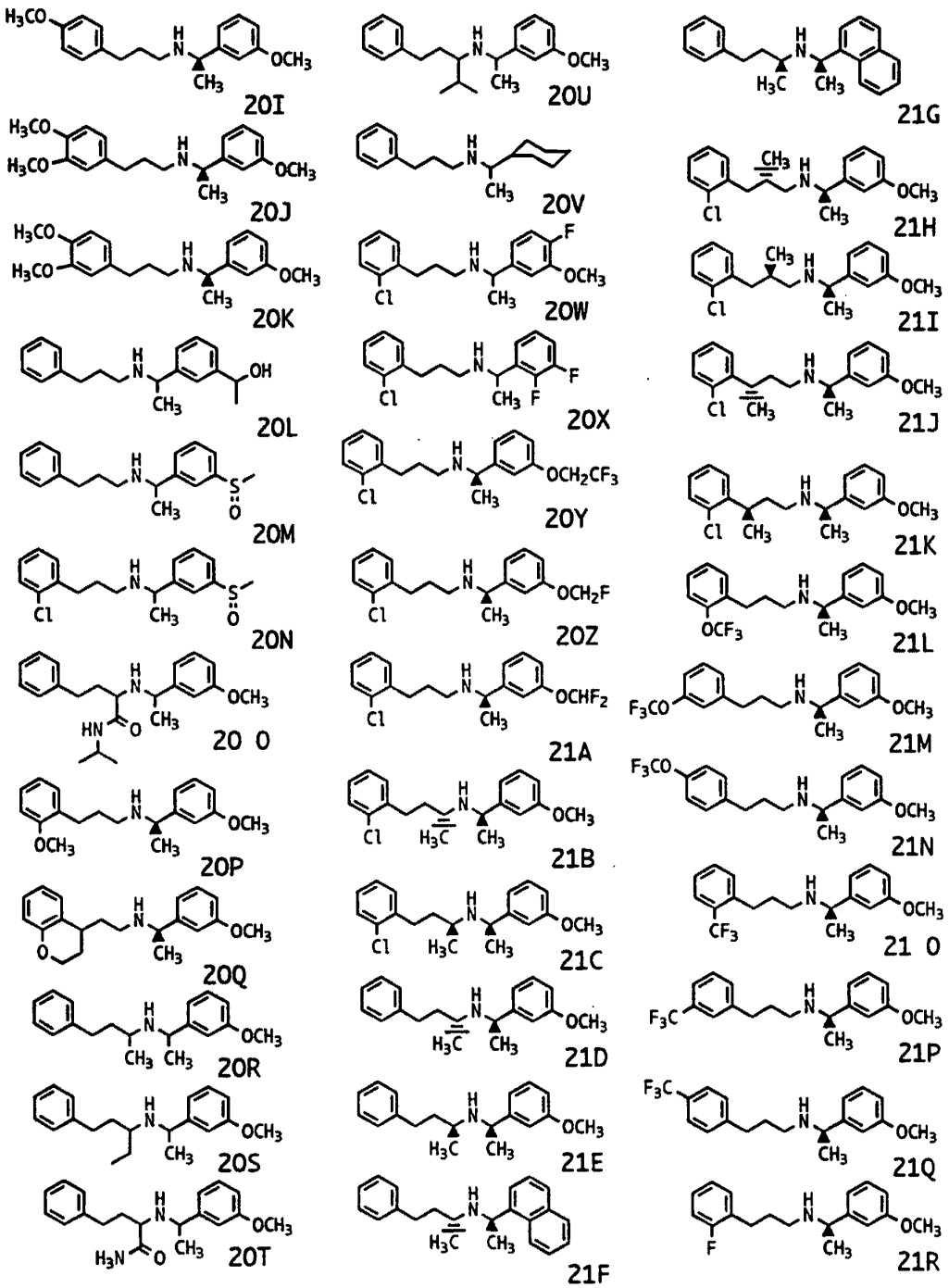
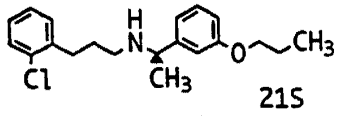


FIG. 1n.

SUBSTITUTE SHEET (RULE 26)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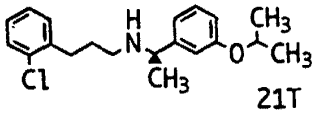
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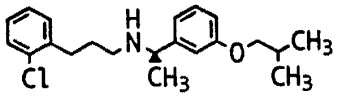
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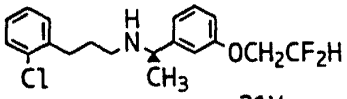
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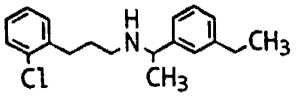
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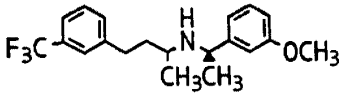
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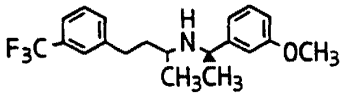
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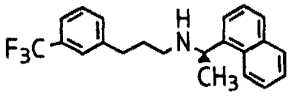
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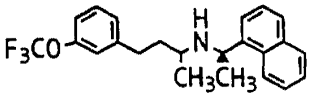
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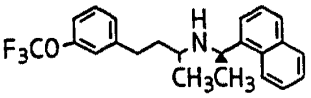
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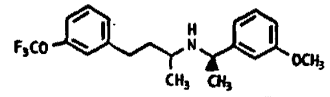
FIG. 1o.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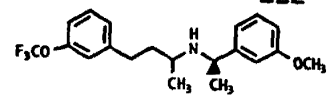
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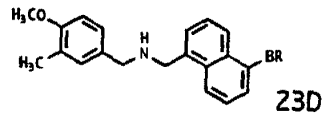
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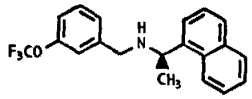
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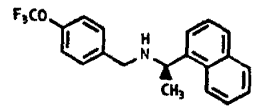
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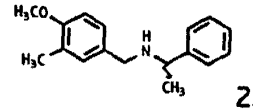
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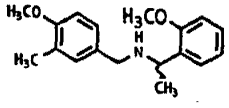
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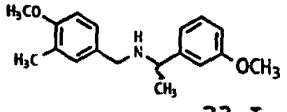
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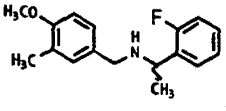
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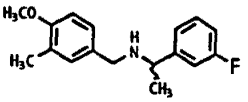
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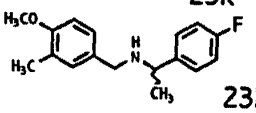
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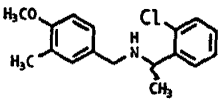
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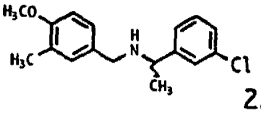
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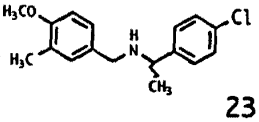
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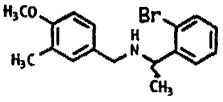
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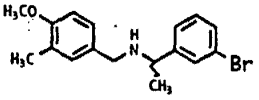
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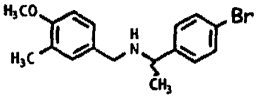
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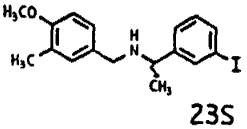
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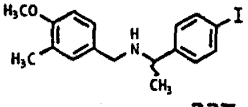
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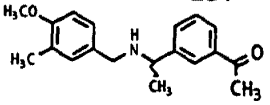
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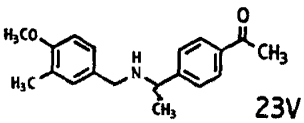
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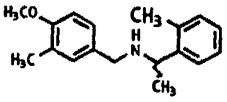
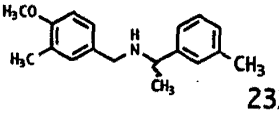
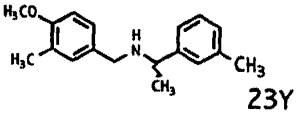
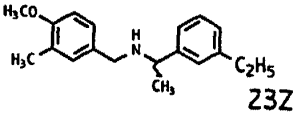
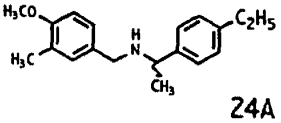
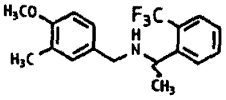

23W

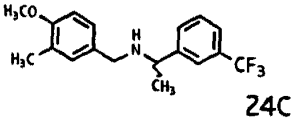

23X

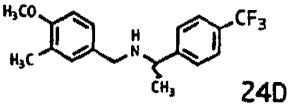

23Y

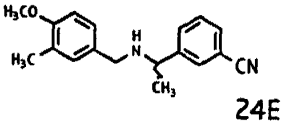

23Z


24A


24B


24C


24D


24E

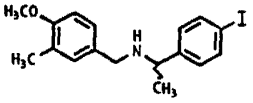

24F

FIG. 1p.

SUBSTITUTE SHEET (RULE 26)

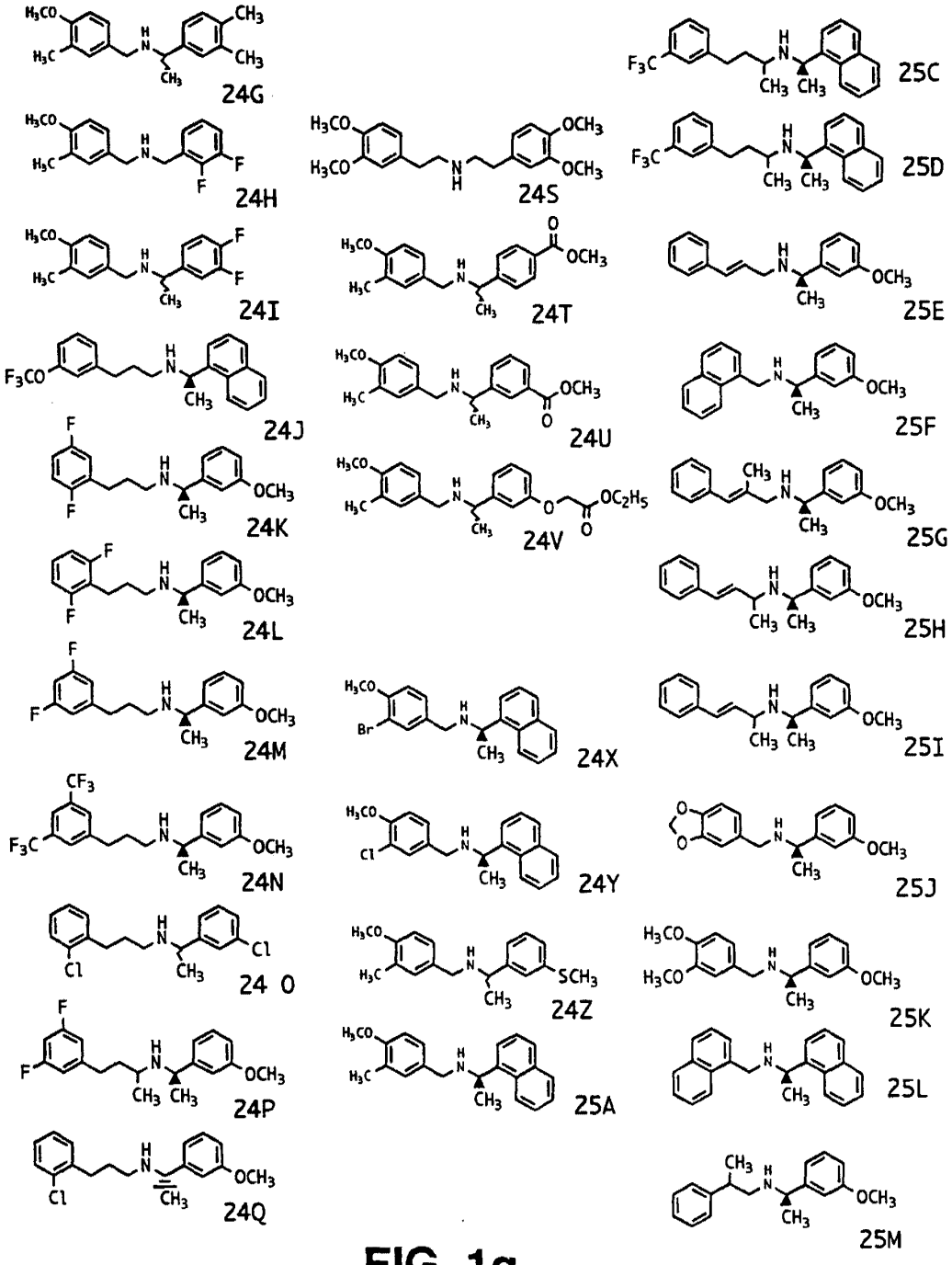


FIG. 1q.

SUBSTITUTE SHEET (RULE 26)

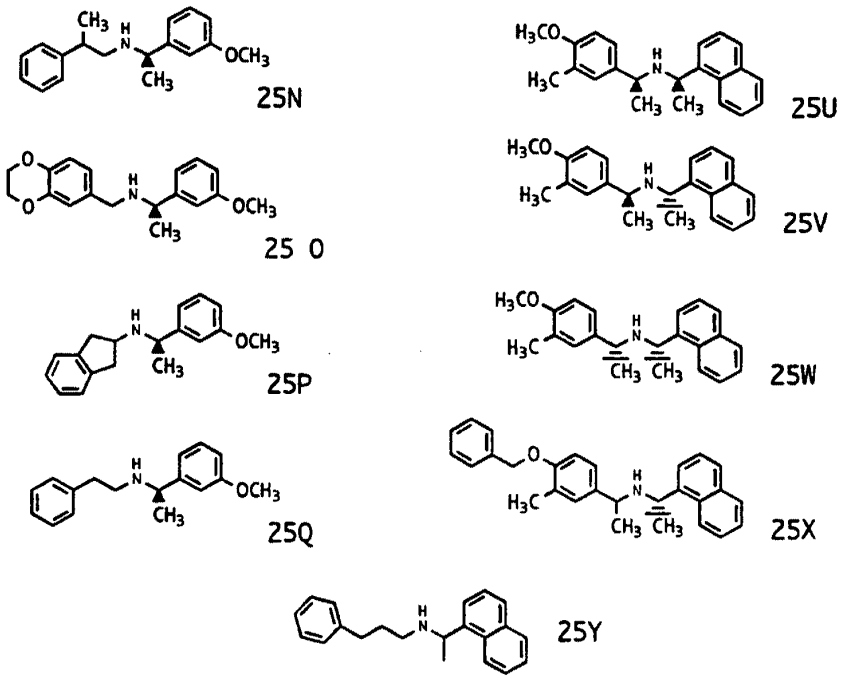
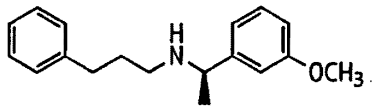


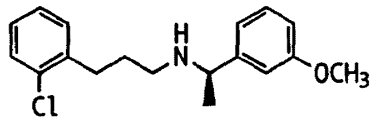
FIG. 1r.



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 ($CDCl_3$) δ1.83 (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 ($CDCl_3$) δ20.3, 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.



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 ($CDCl_3$) δ1.85 (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 ($CDCl_3$) δ20.2, 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.

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

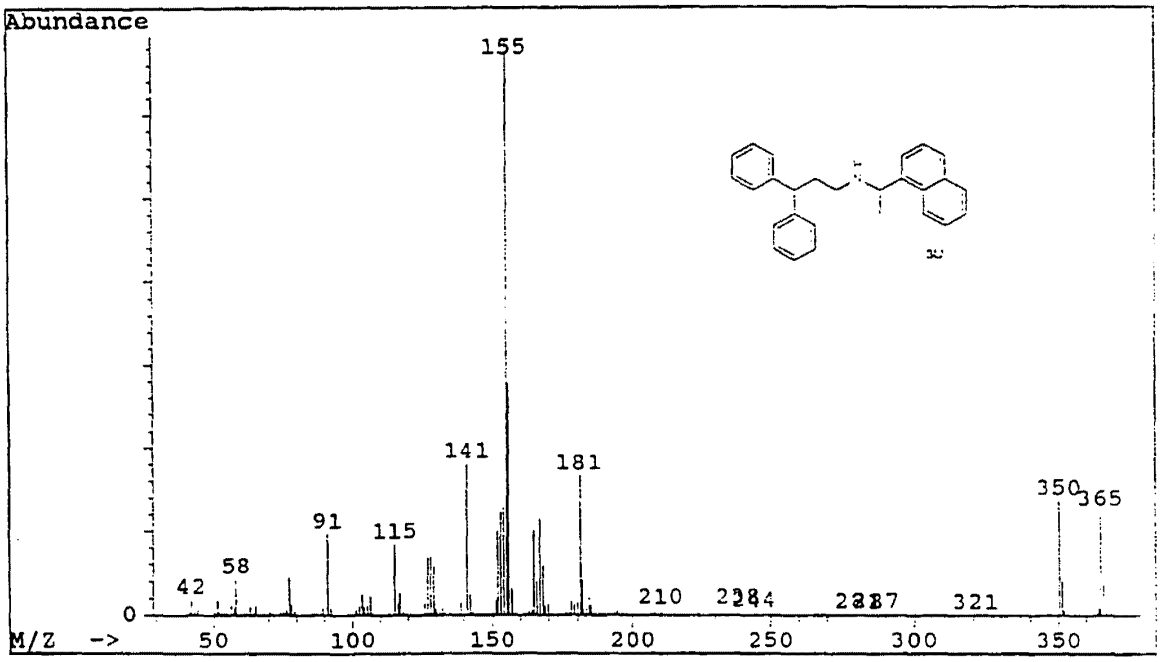
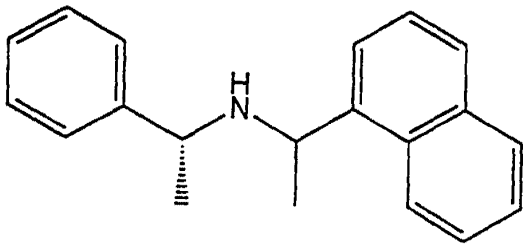


FIGURE 4

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4G

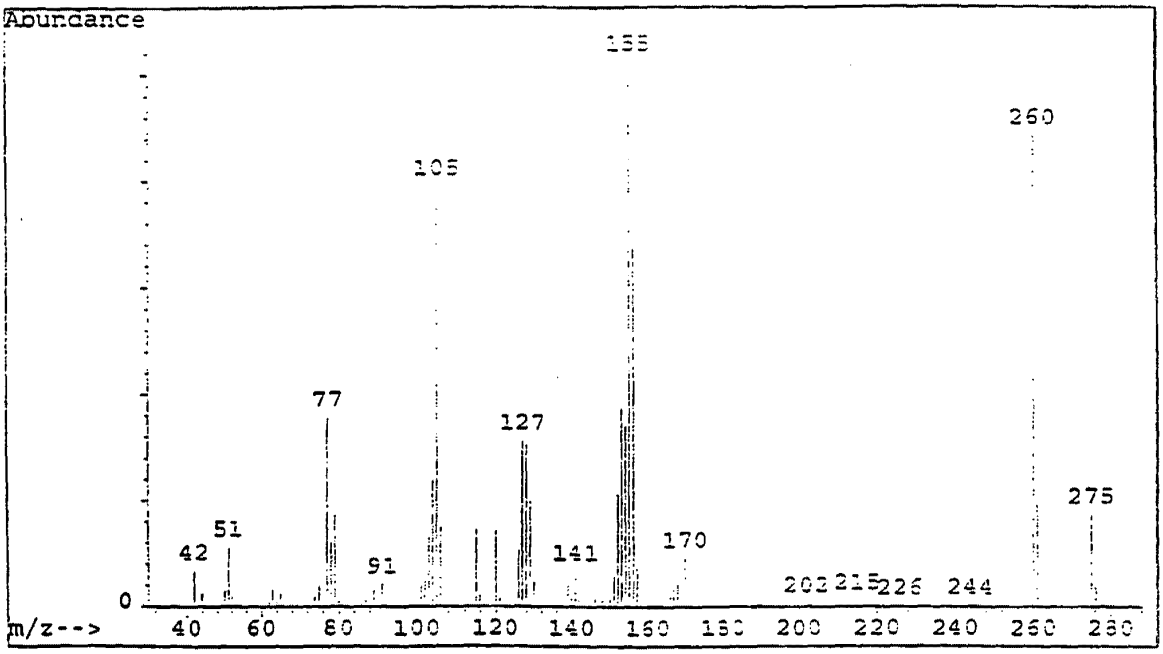
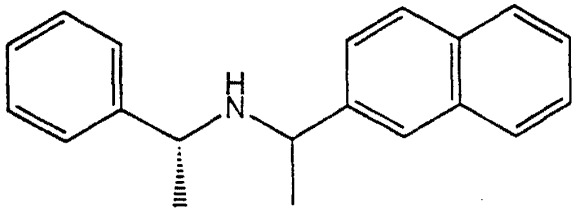


FIGURE 5

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4H

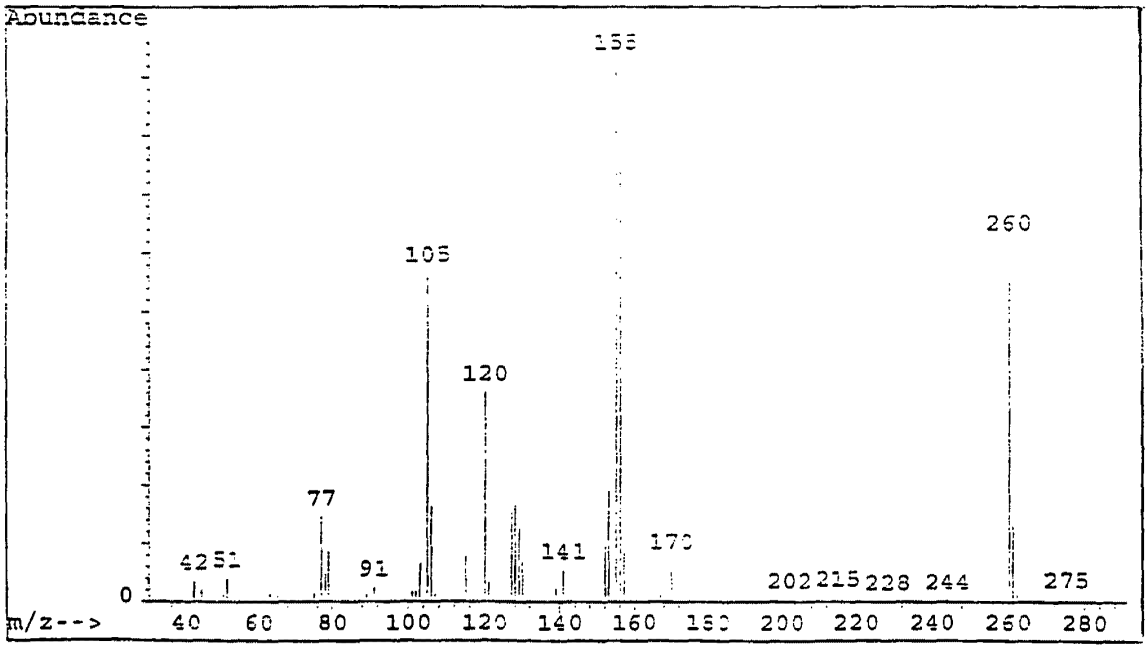
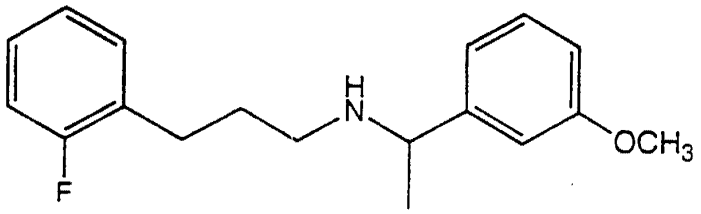


FIGURE 6

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4M

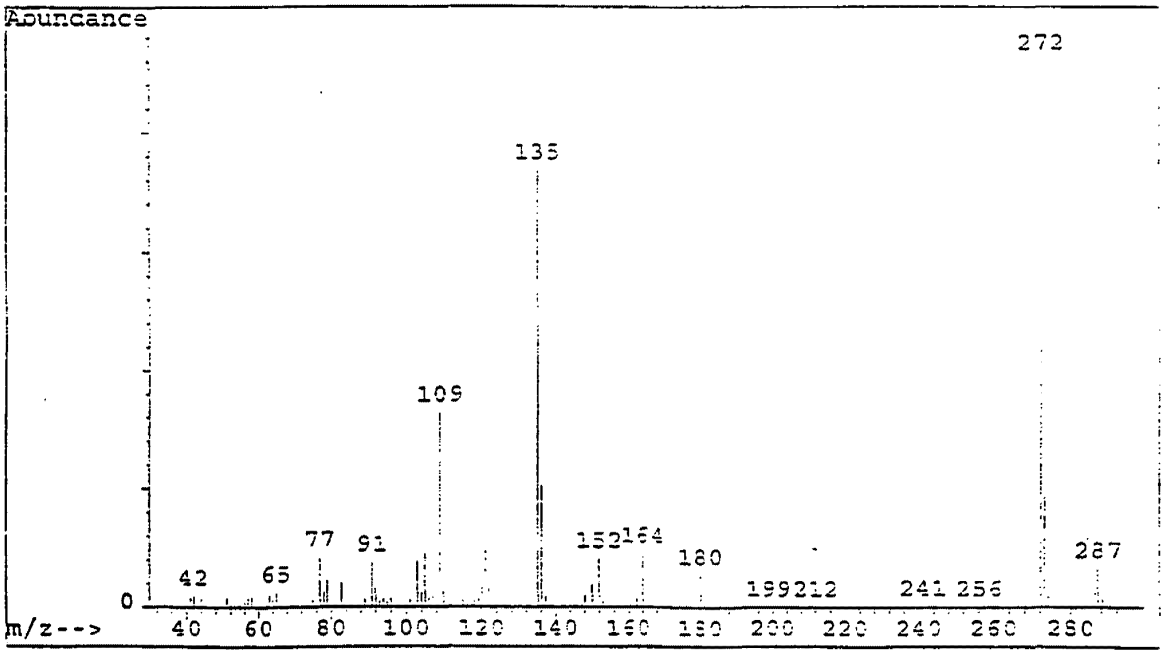
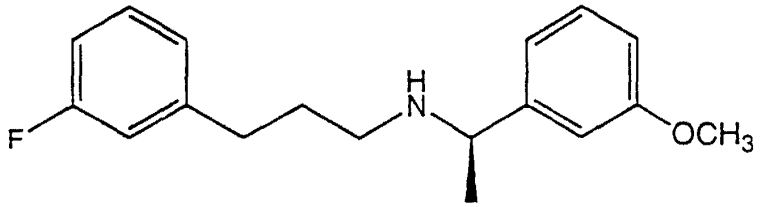


FIGURE 7

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4N

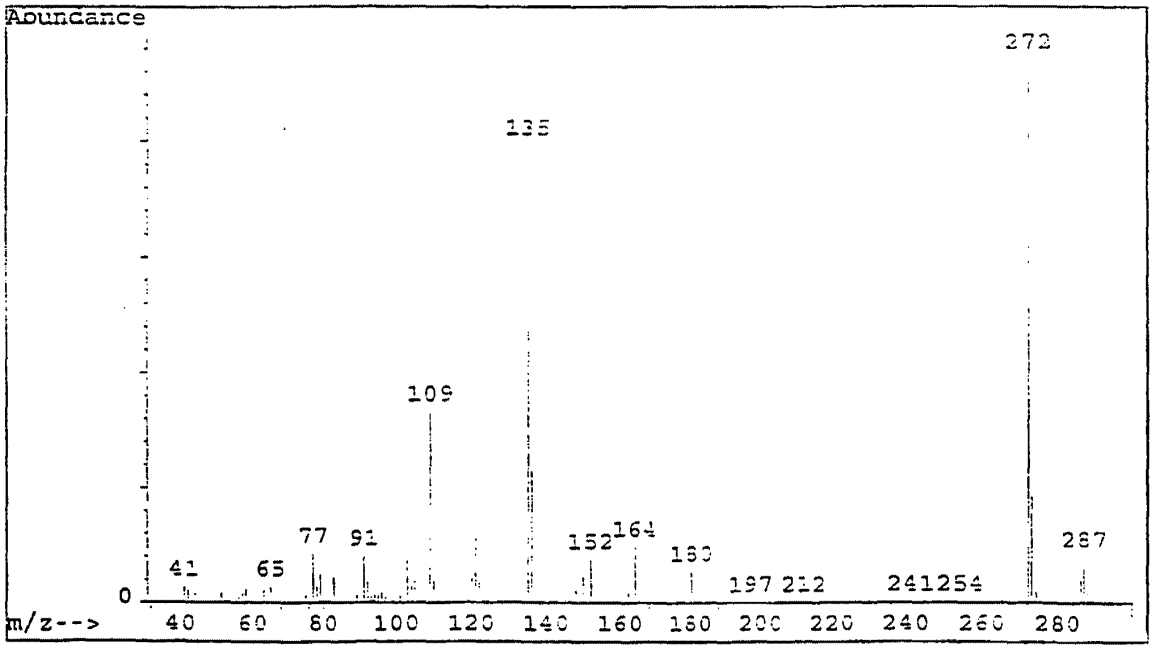
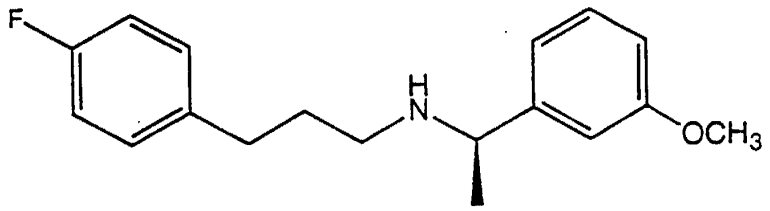


FIGURE 8

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4P

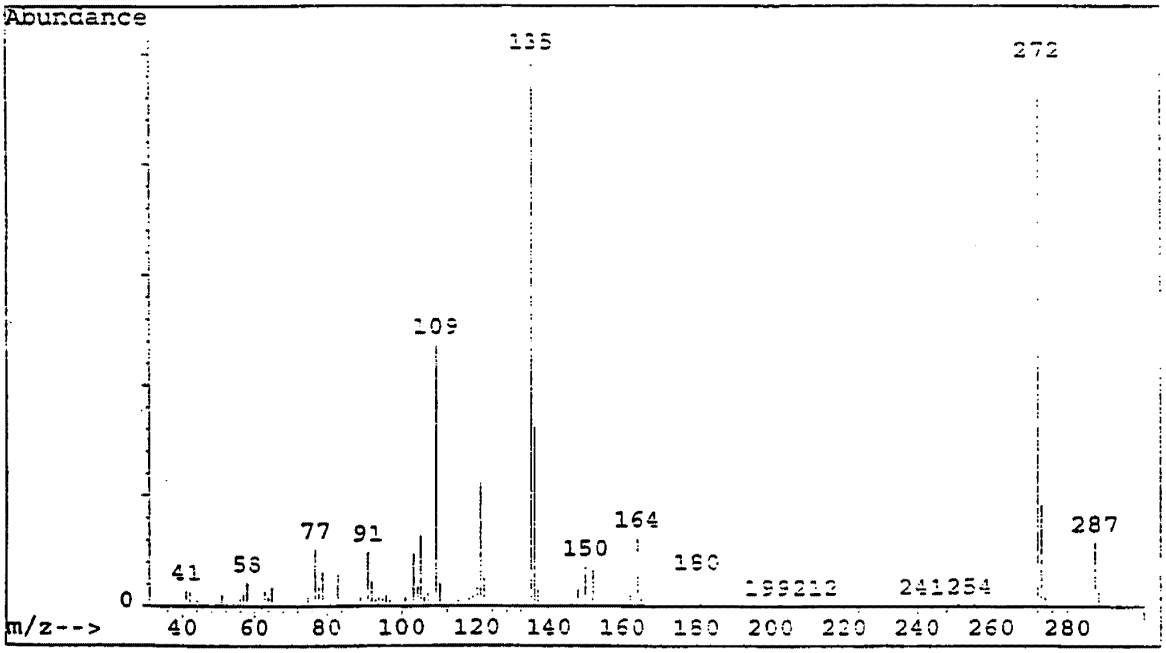
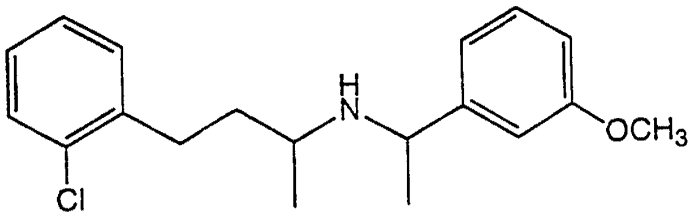


FIGURE 9

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4T

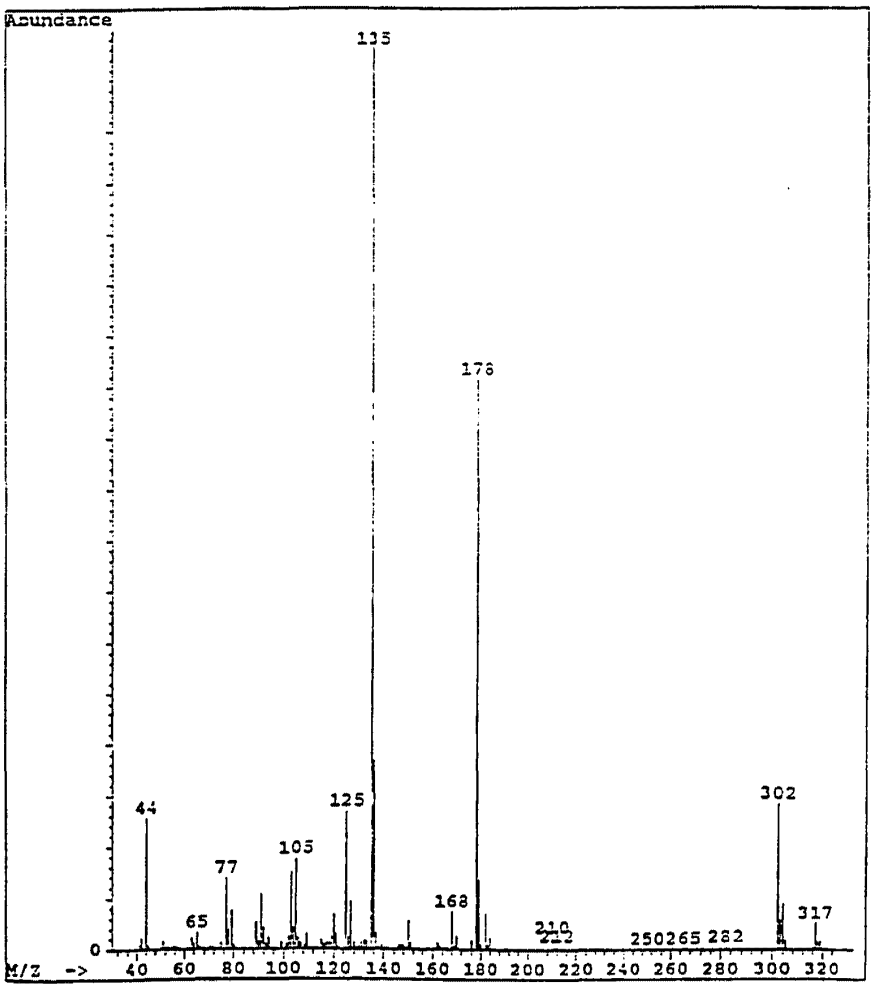
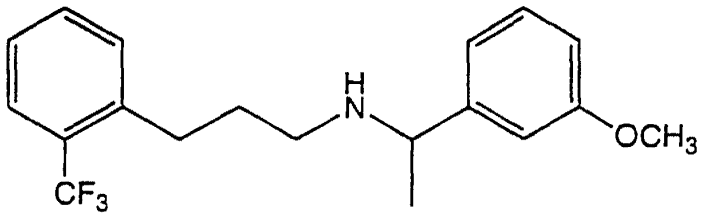


FIGURE 10

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4V

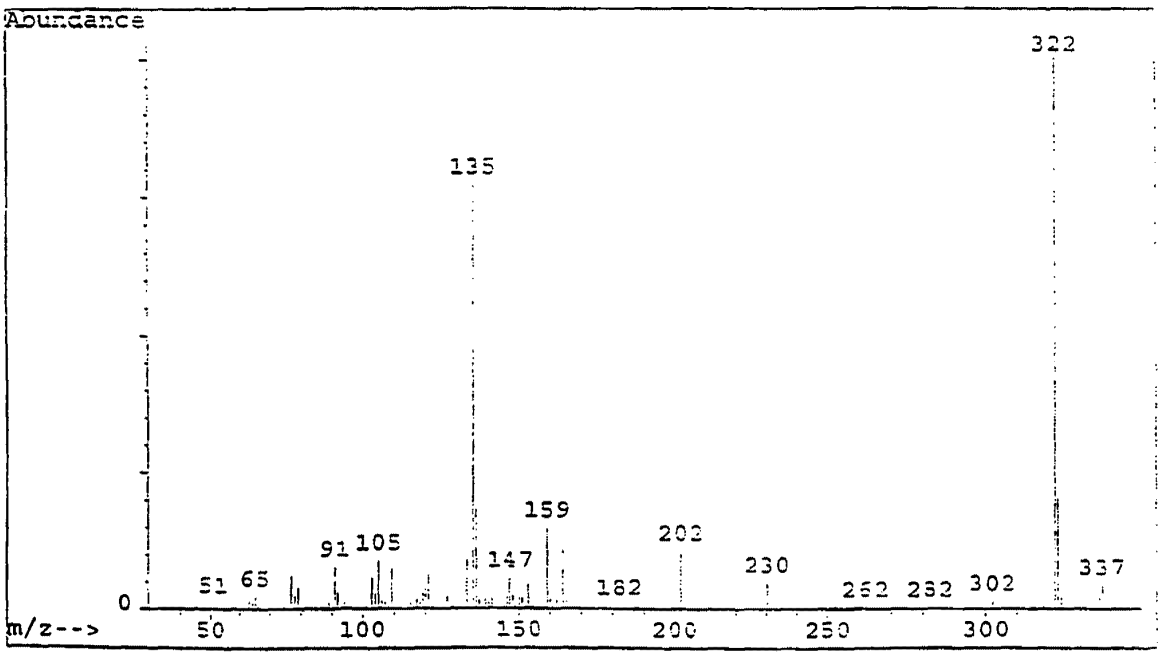
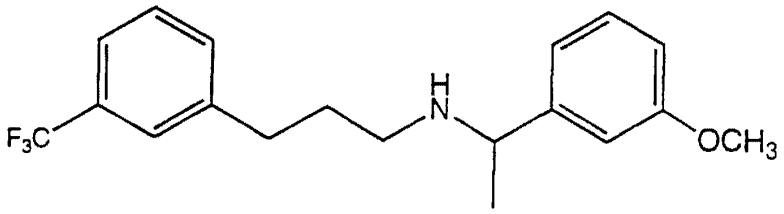


FIGURE 11

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4W

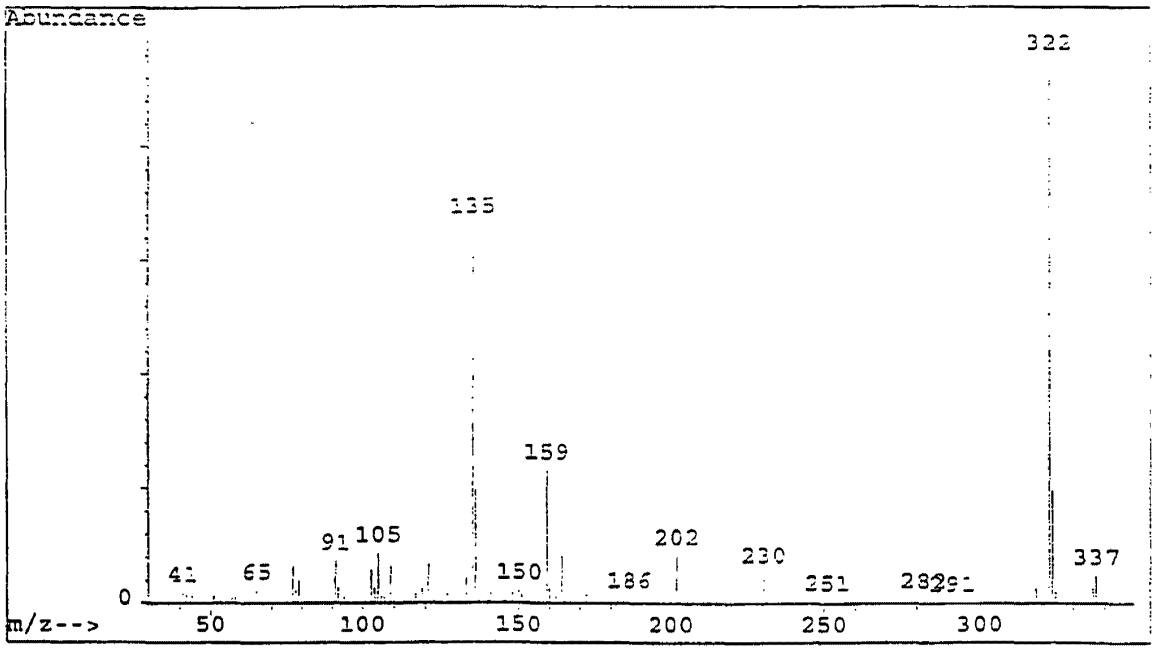
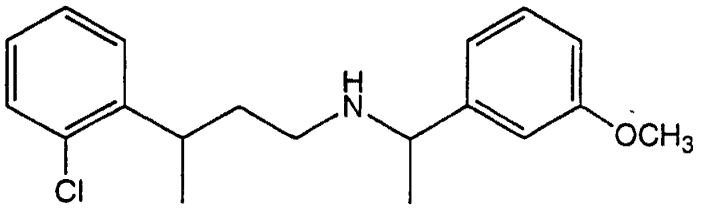


FIGURE 12

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4Y

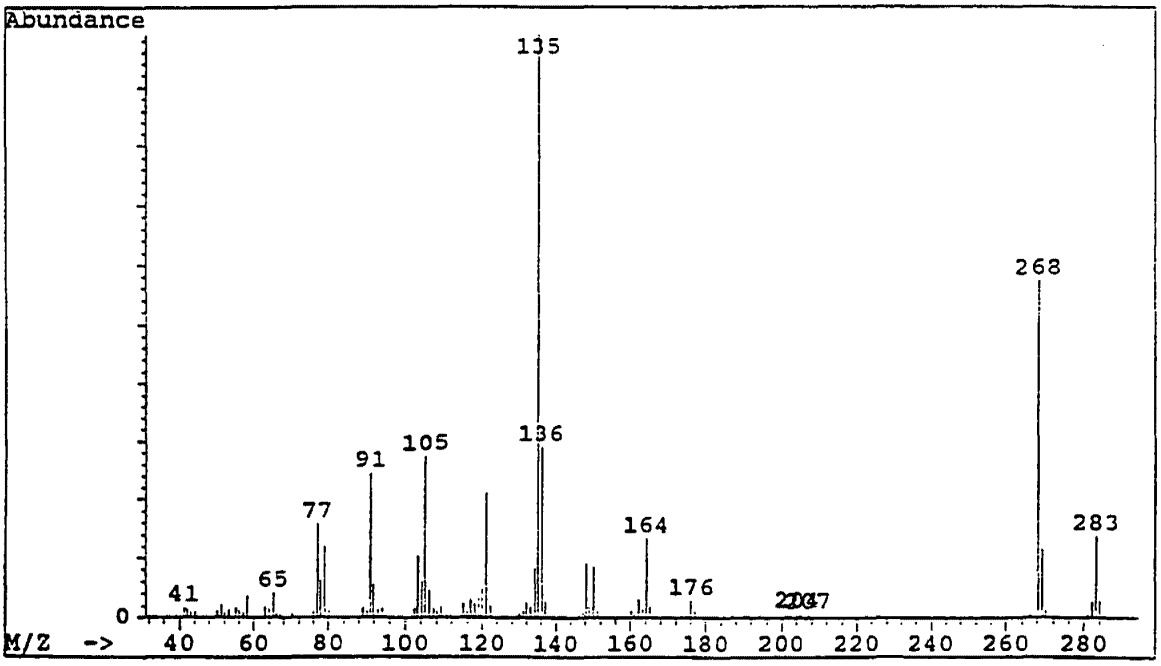
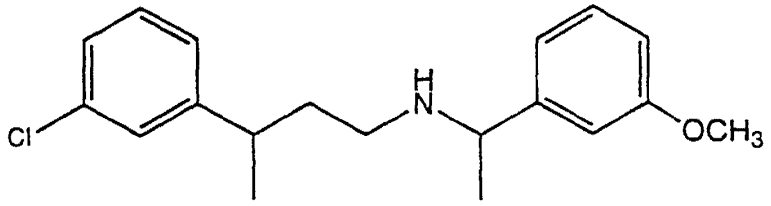


FIGURE 13

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



4Z

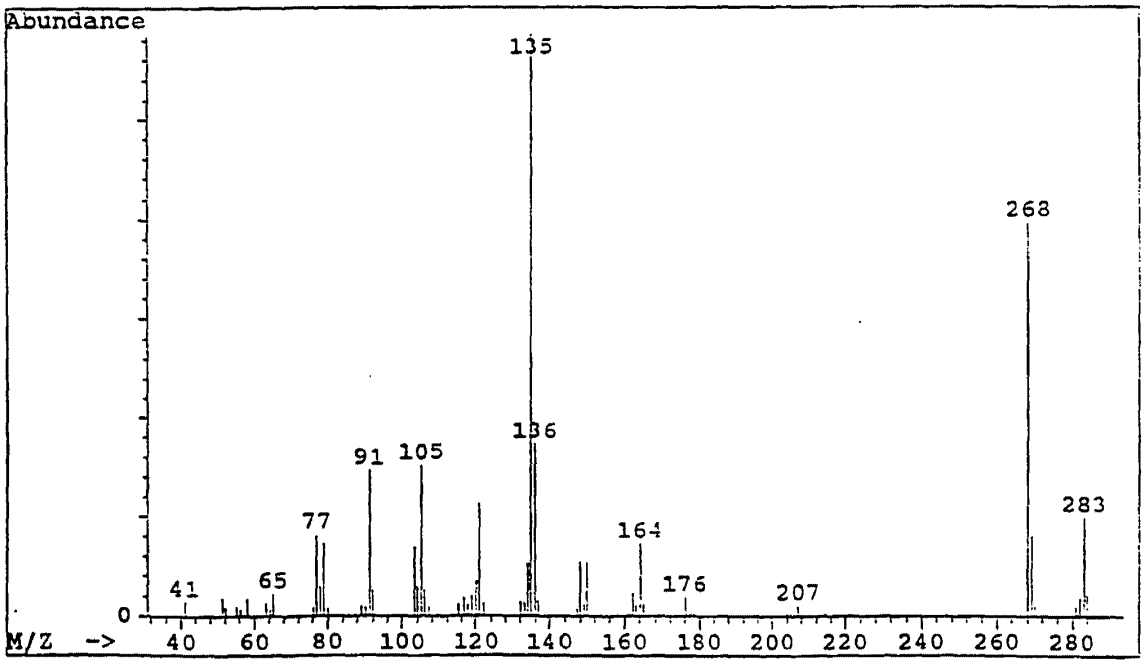
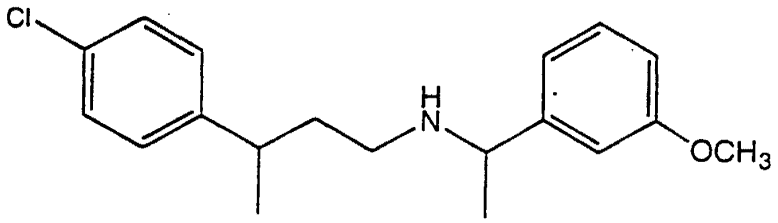


FIGURE 14

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



5C

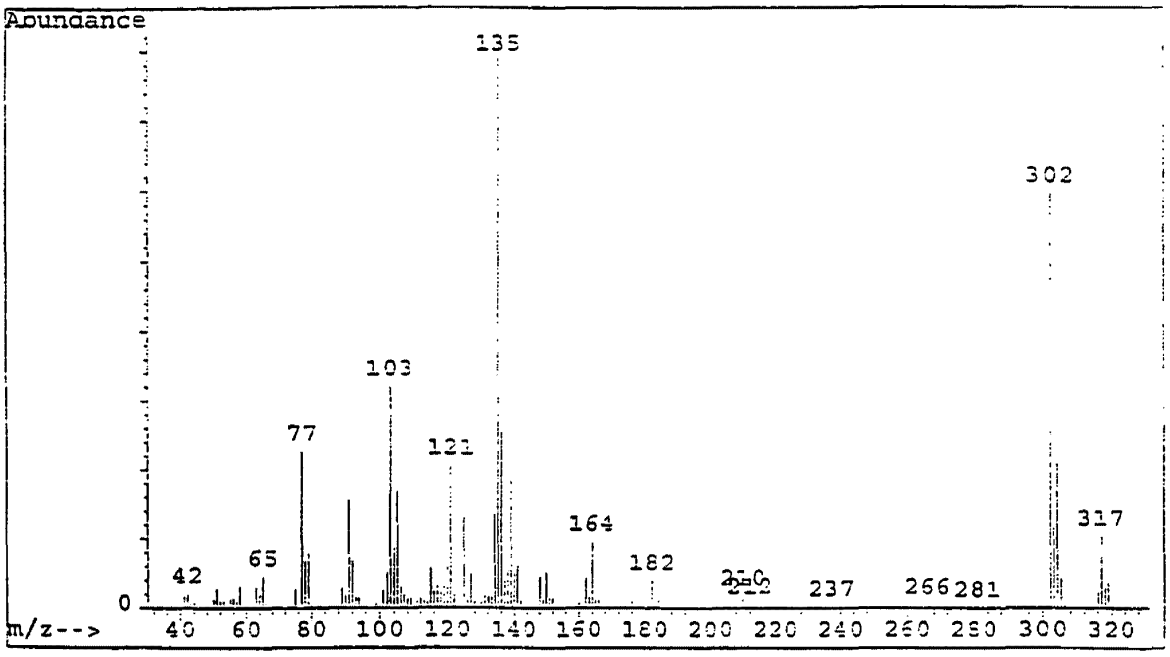
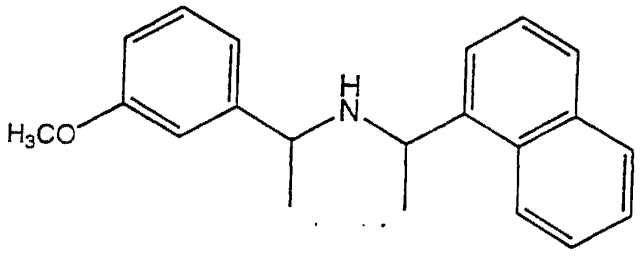


FIGURE 15

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



6E

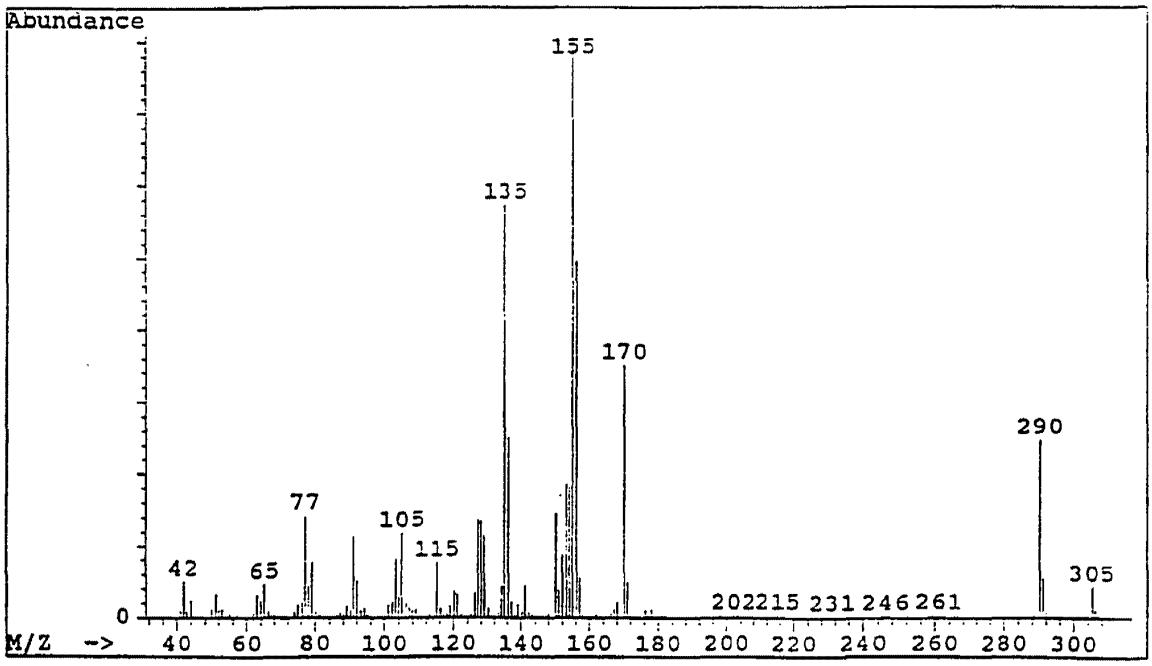
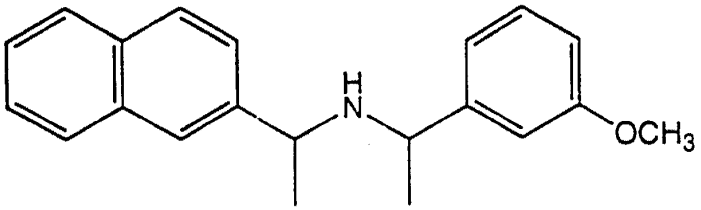


FIGURE 16

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



6F

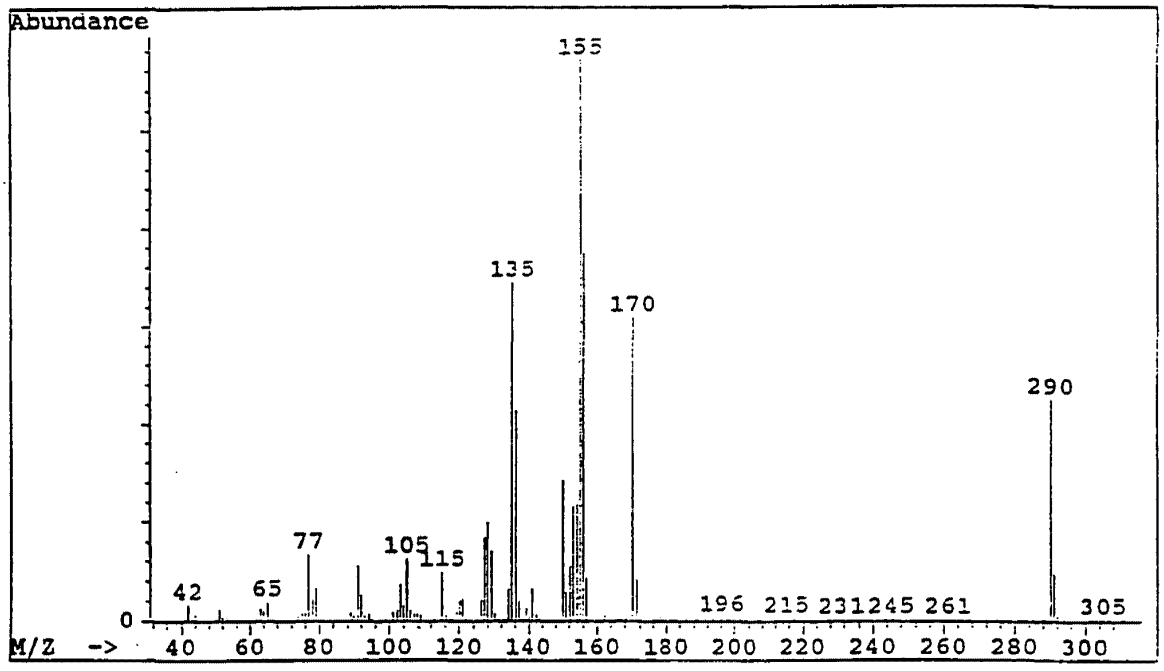
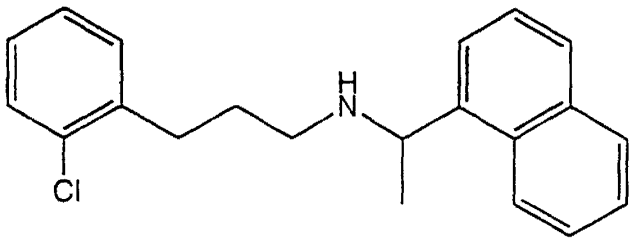


FIGURE 17

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



61

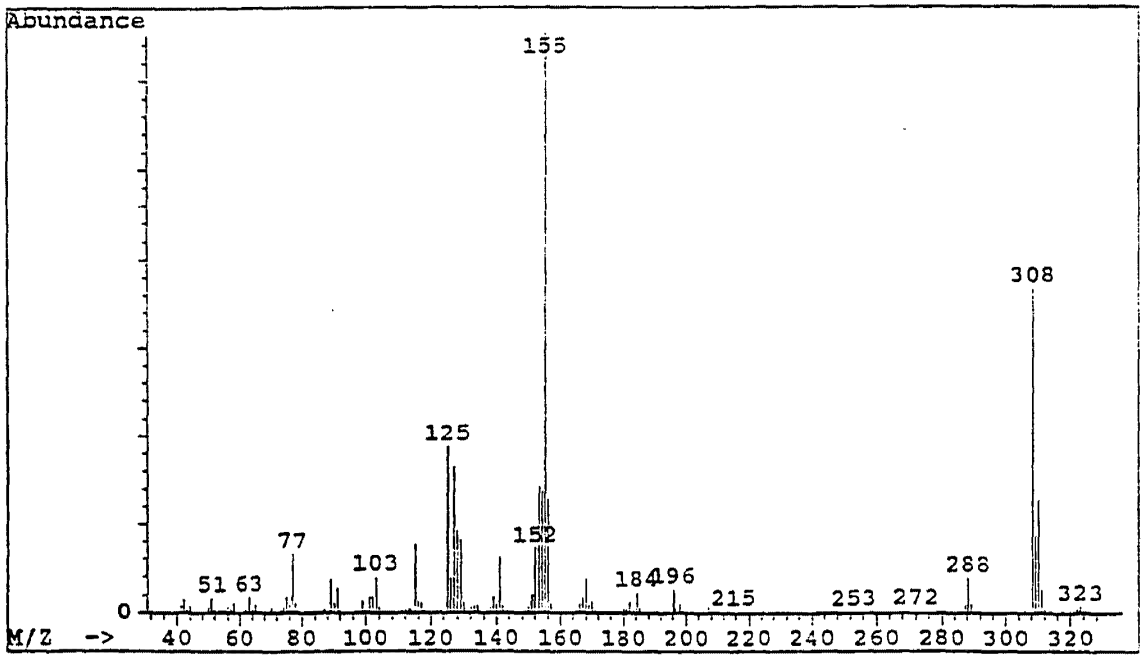
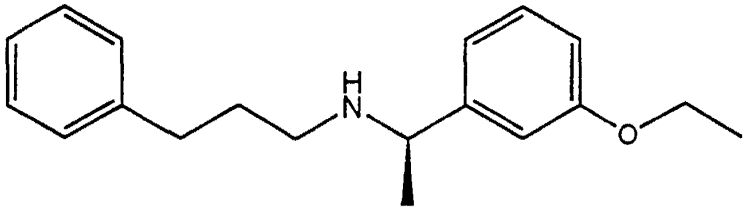


FIGURE 18

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



6R

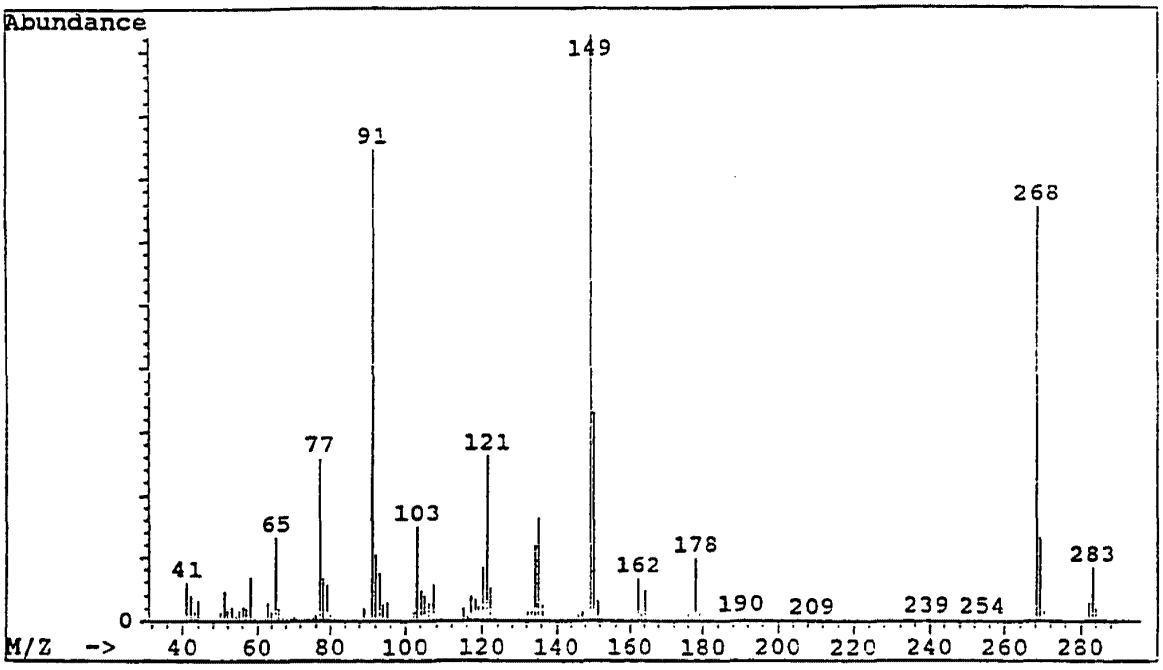
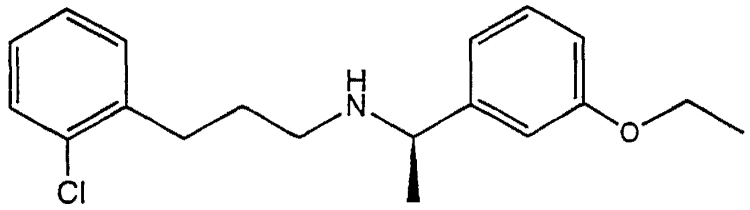


FIGURE 19

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



6T

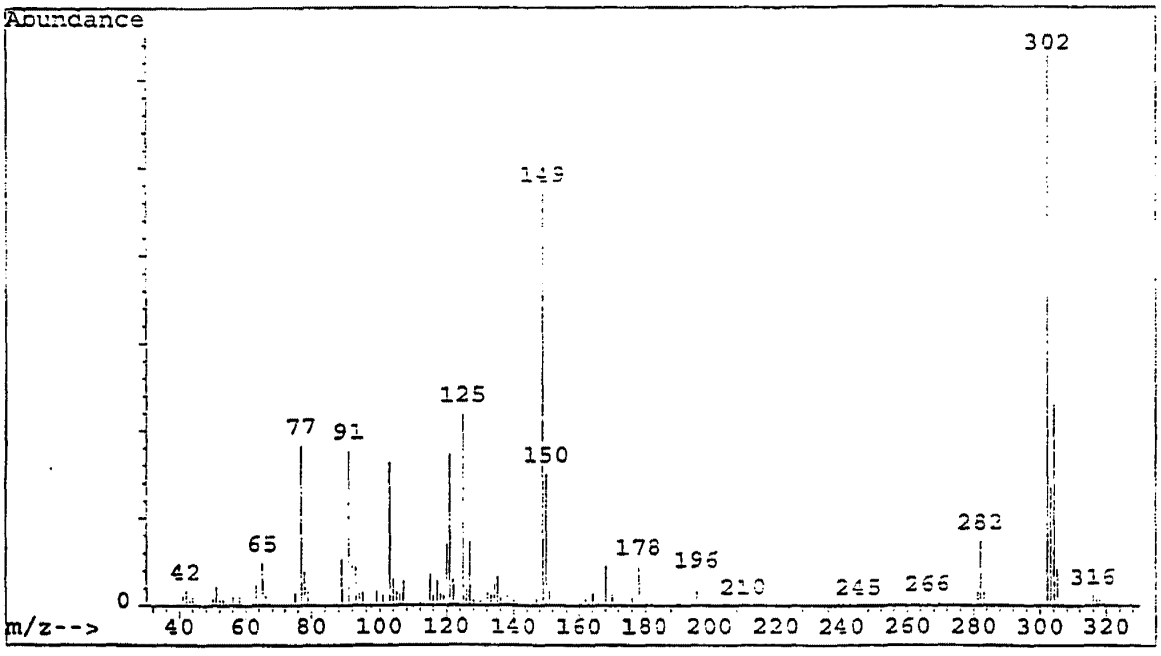
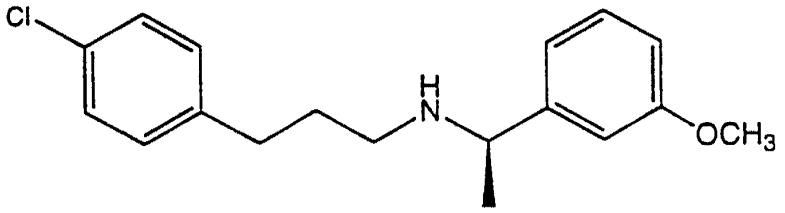


FIGURE 20

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



6V

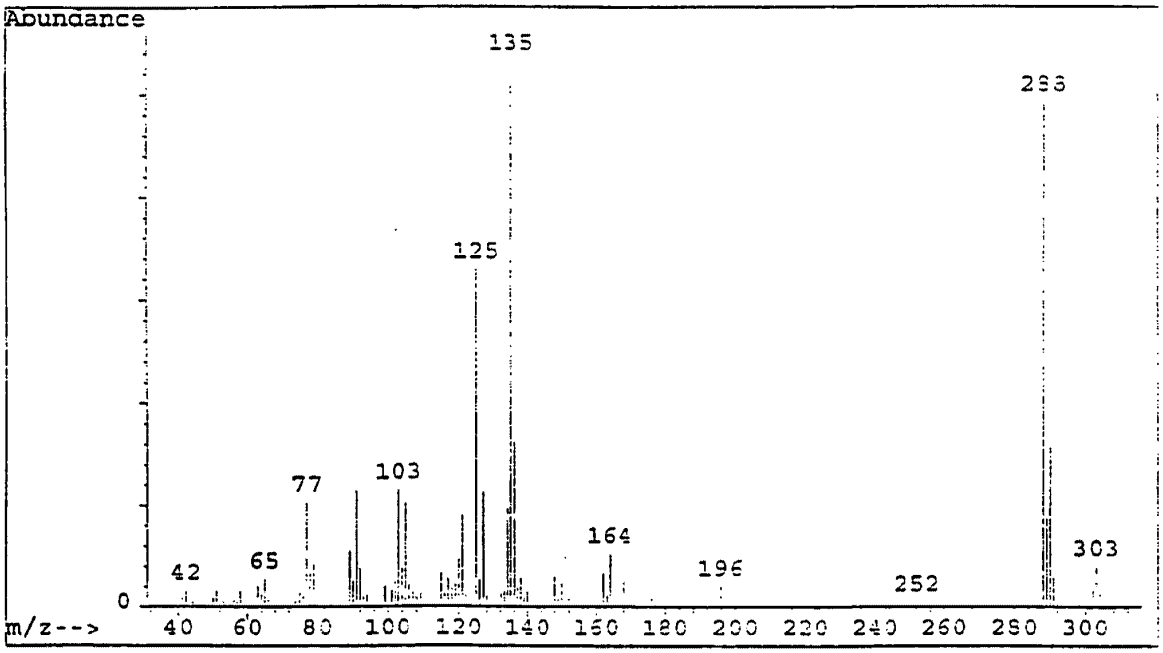
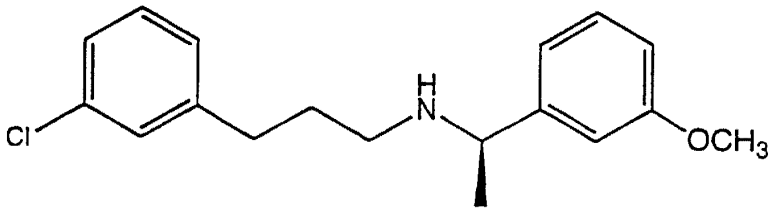


FIGURE 21

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



6X

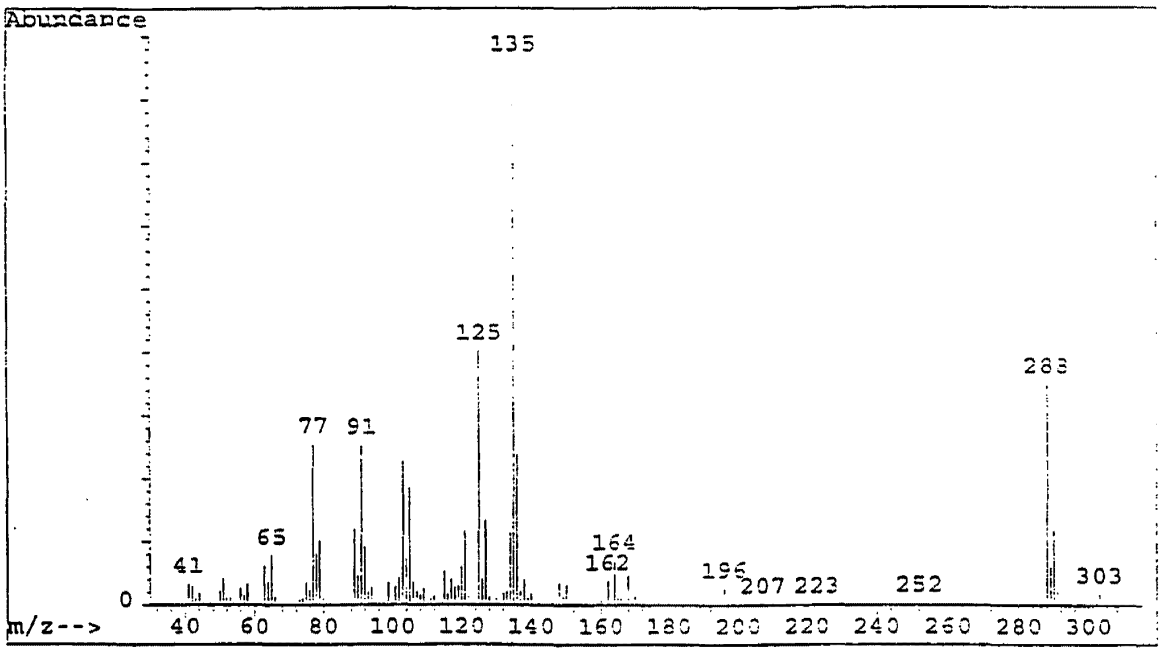
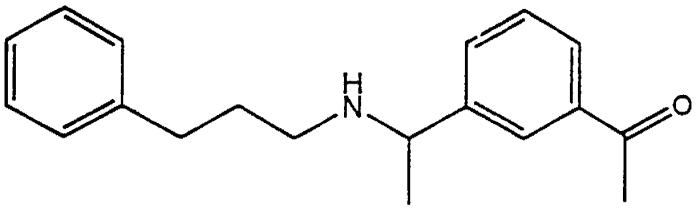


FIGURE 22

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



7W

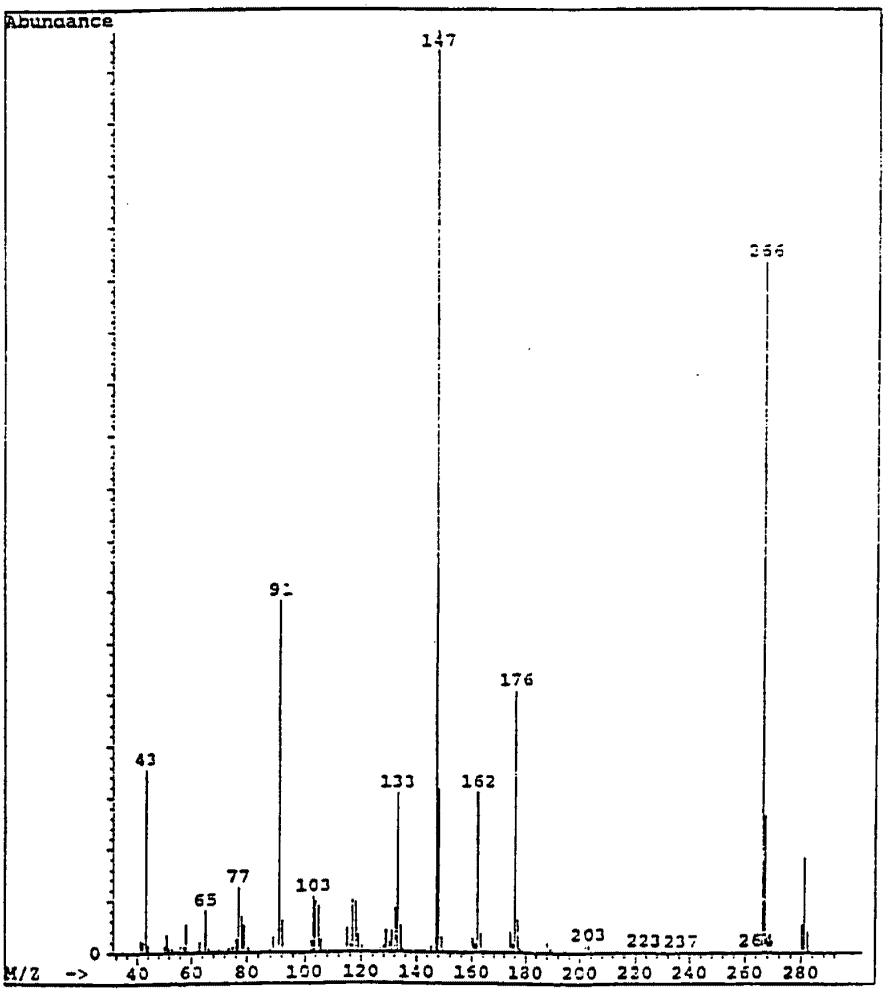
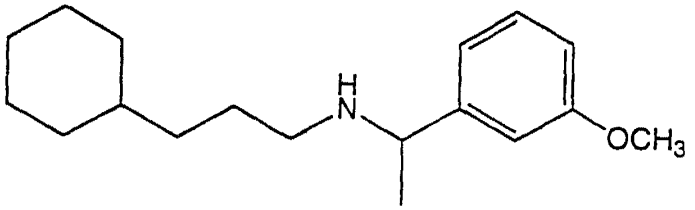


FIGURE 23

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



7X

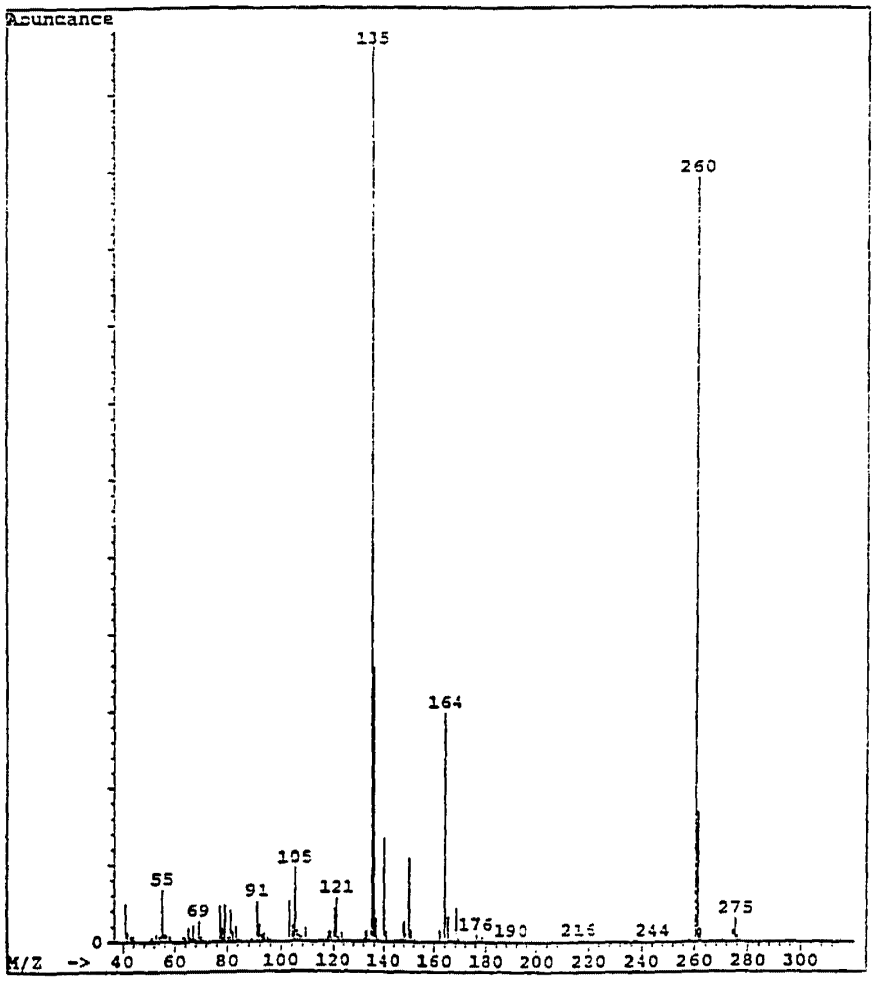
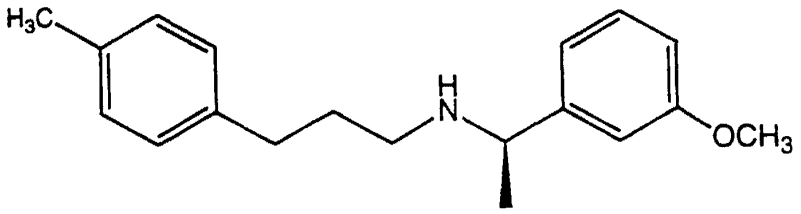


FIGURE 24

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



8X

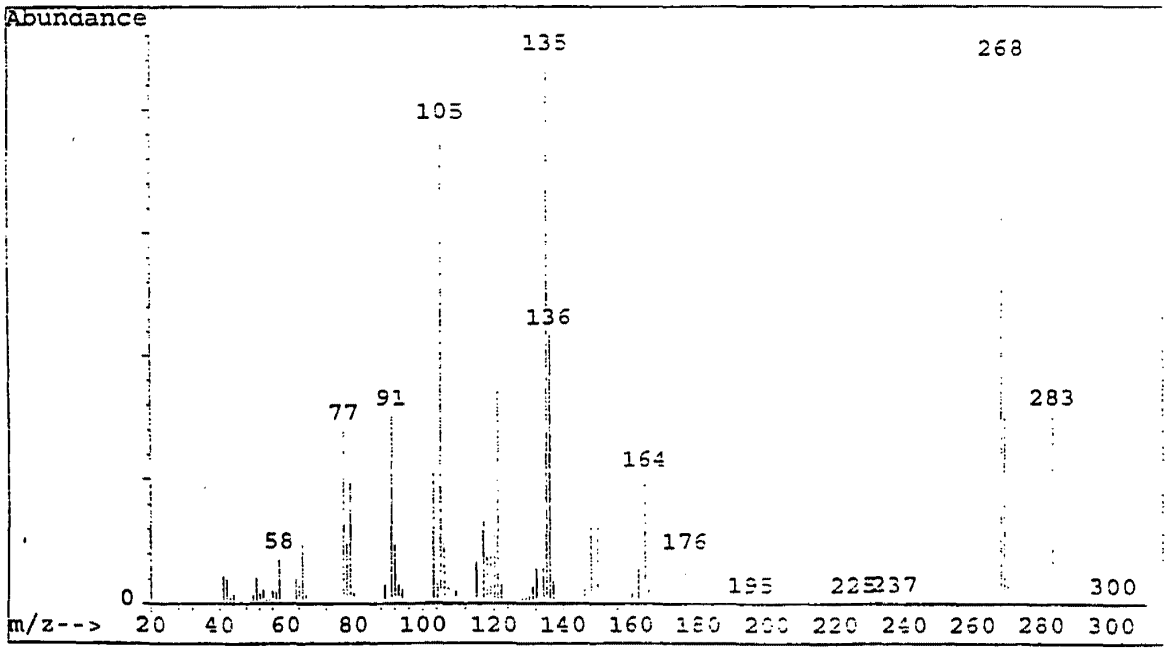


FIGURE 25

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

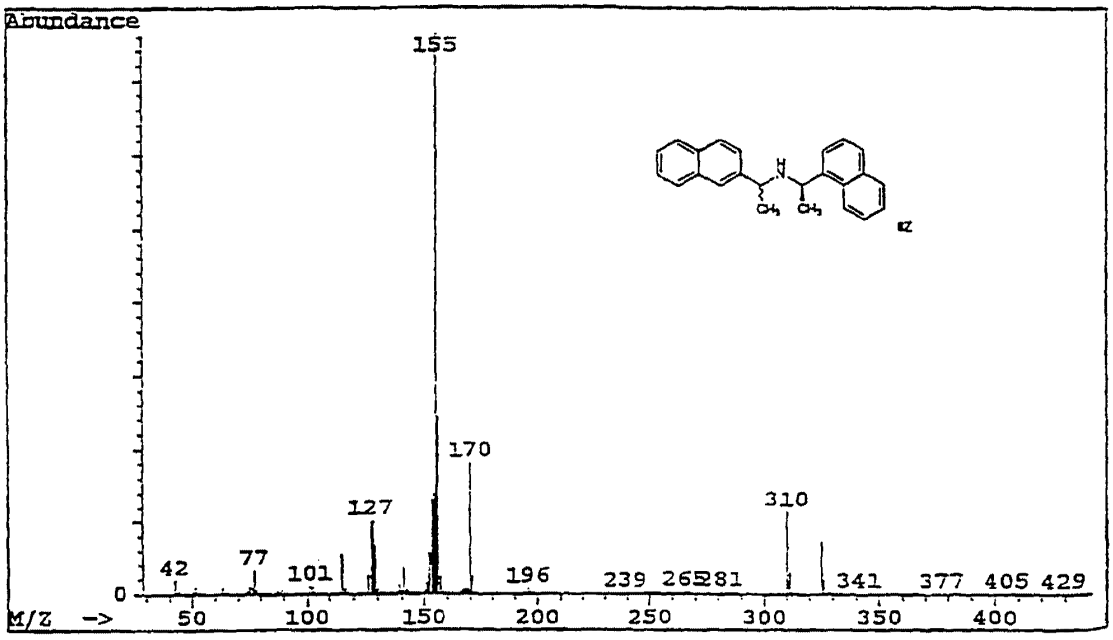


FIGURE 26

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

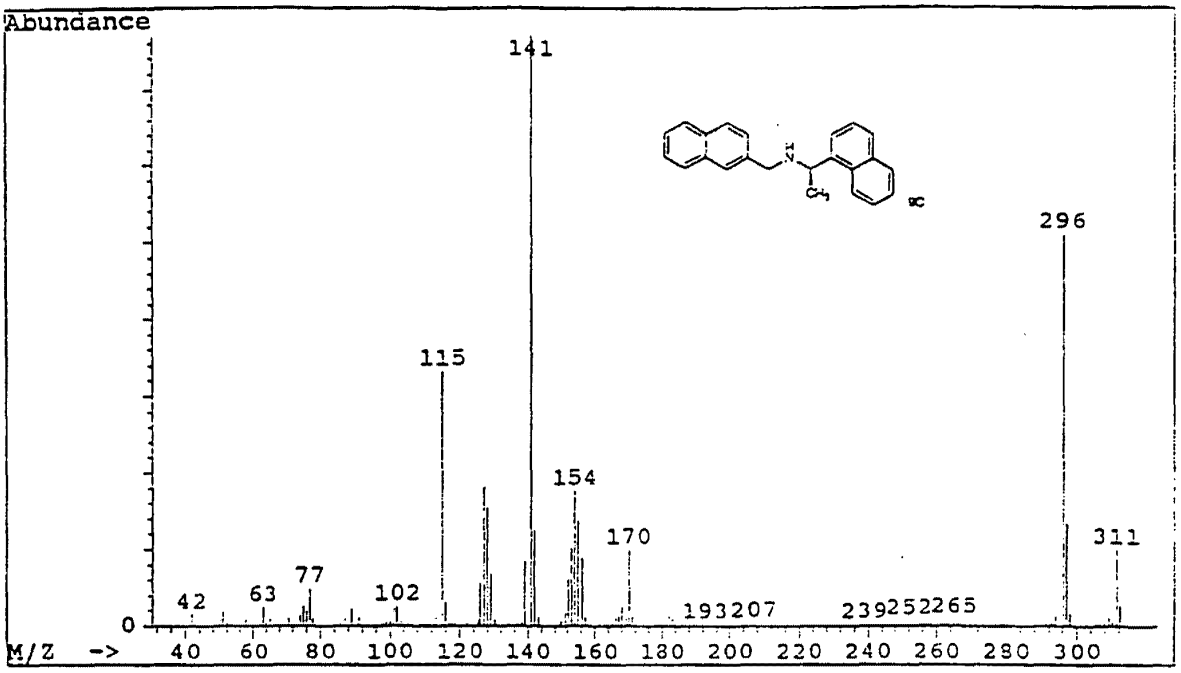


FIGURE 27

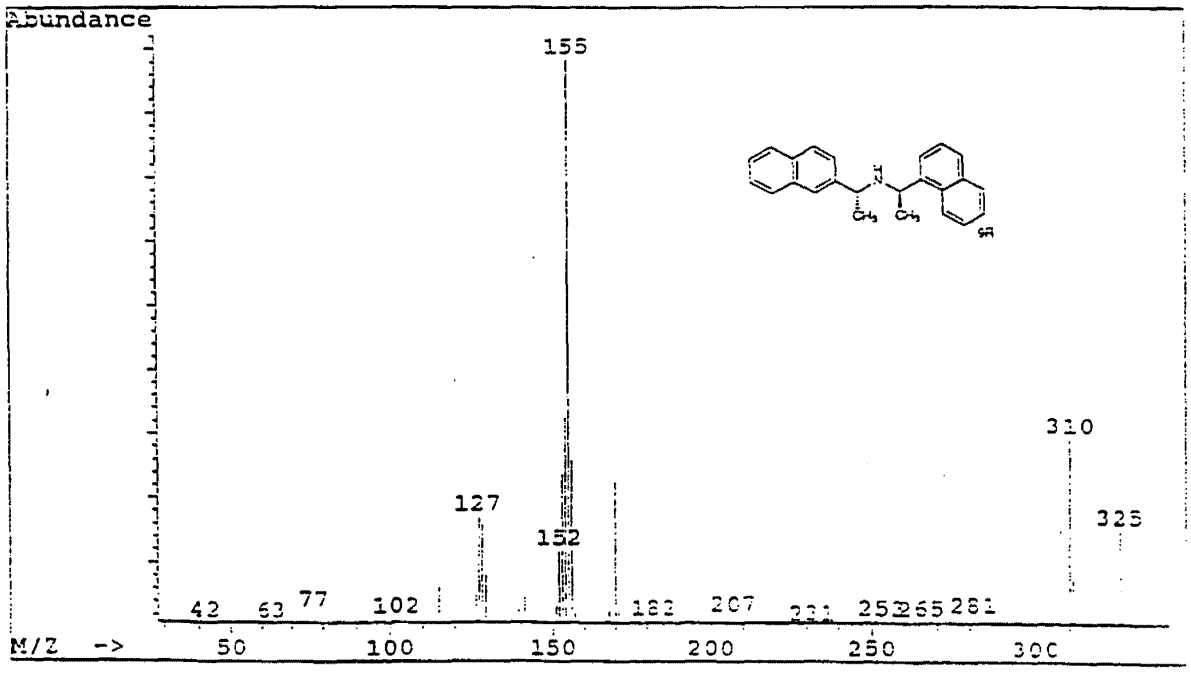


FIGURE 28

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

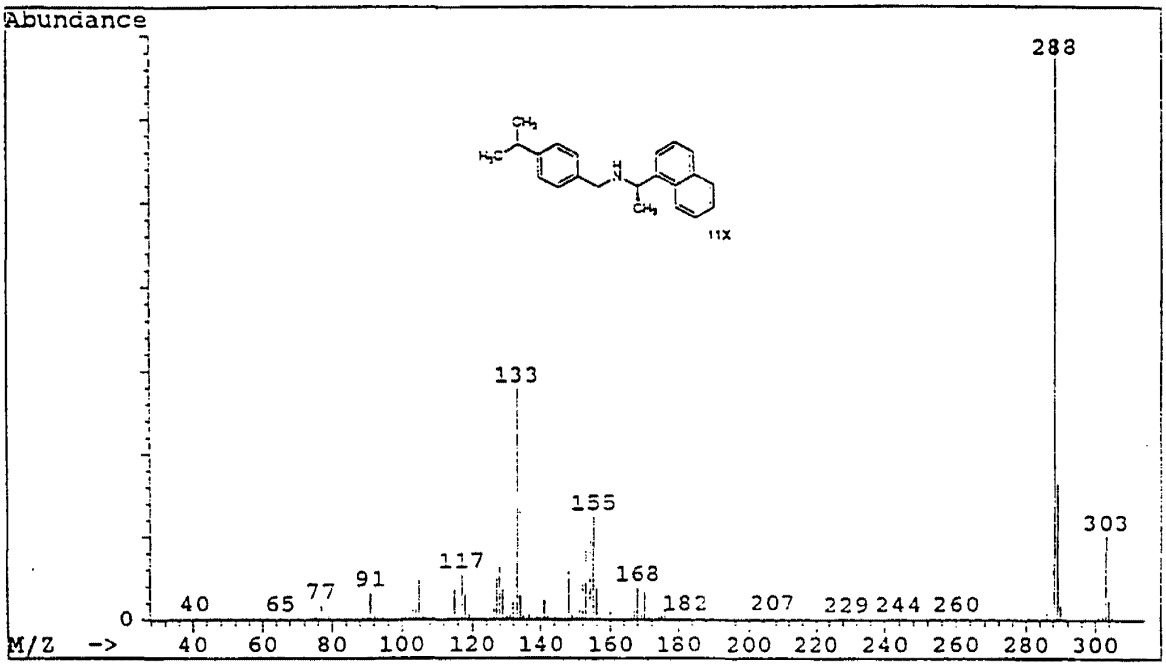


FIGURE 29

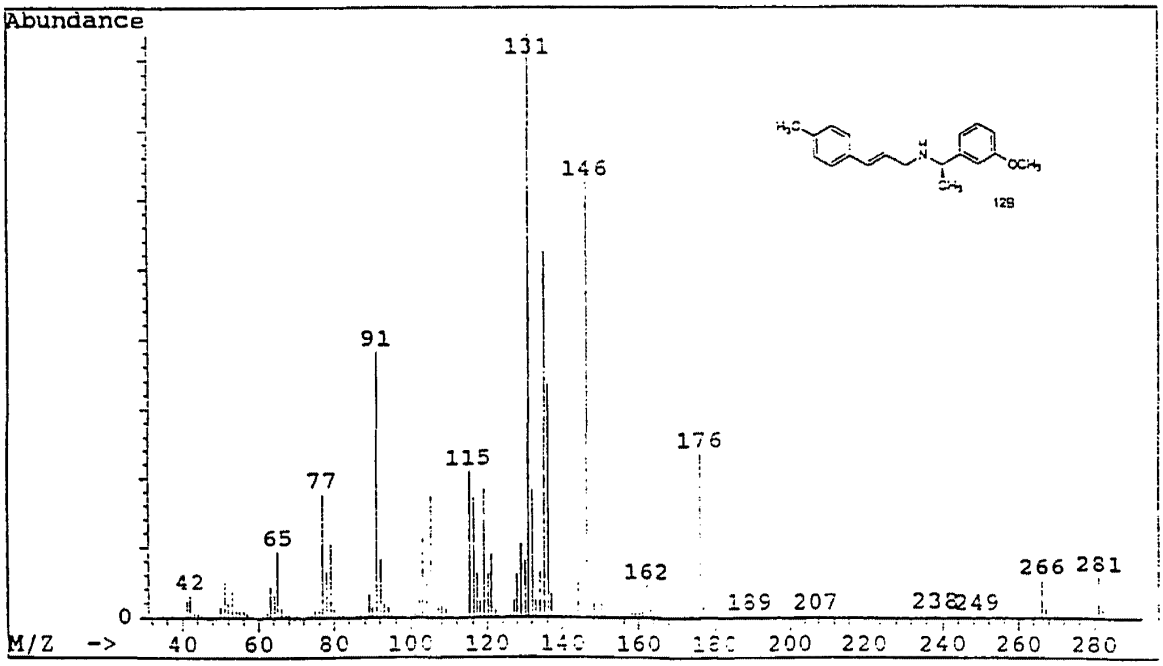


FIGURE 30

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

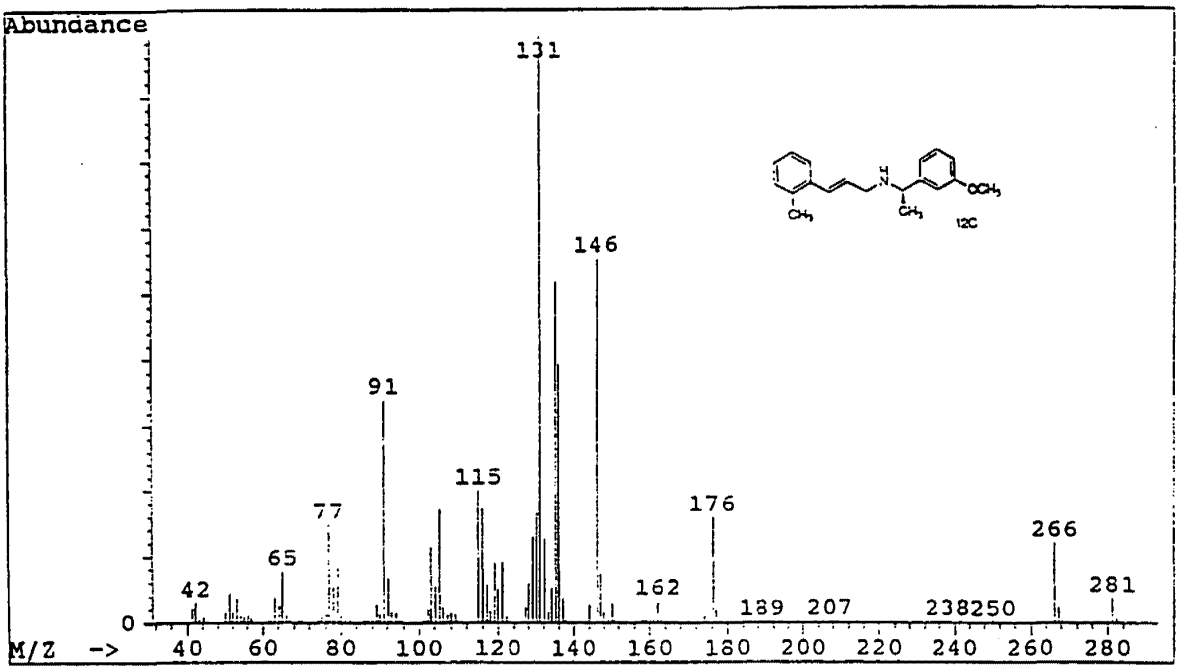


FIGURE 31

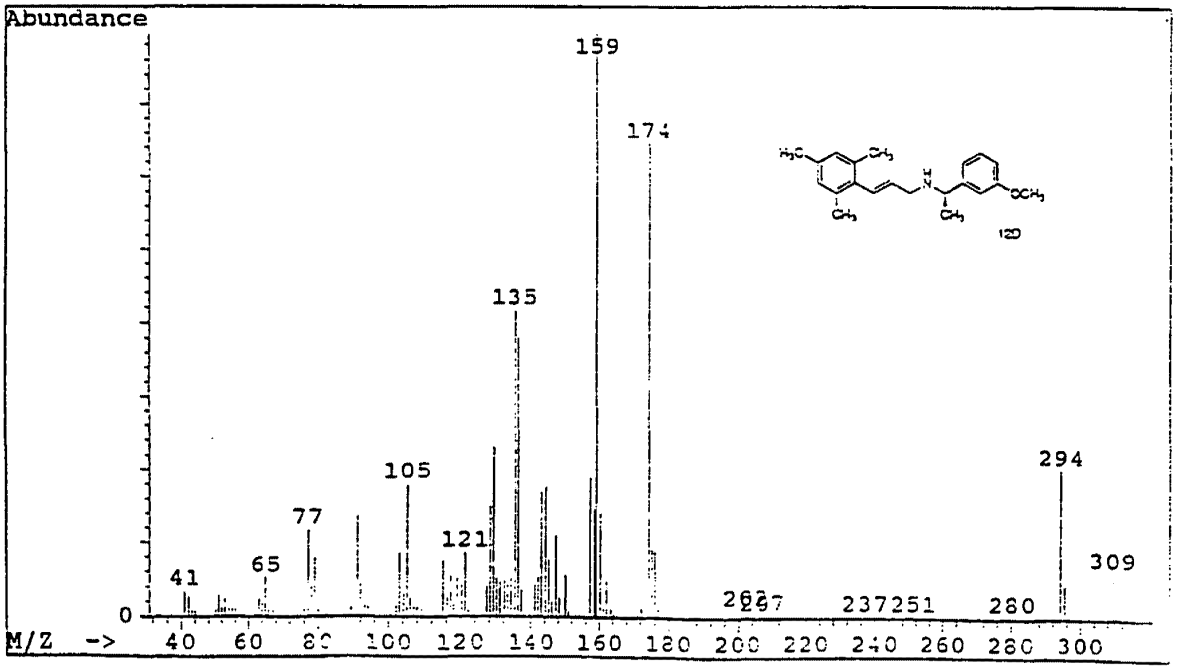


FIGURE 32

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

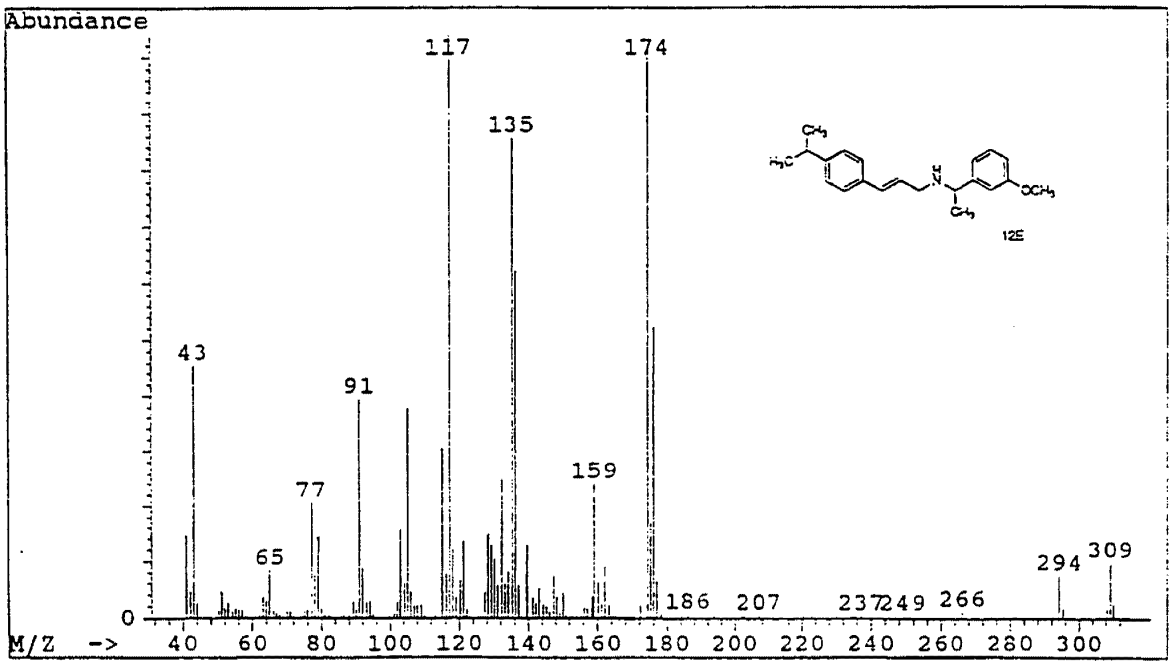


FIGURE 33

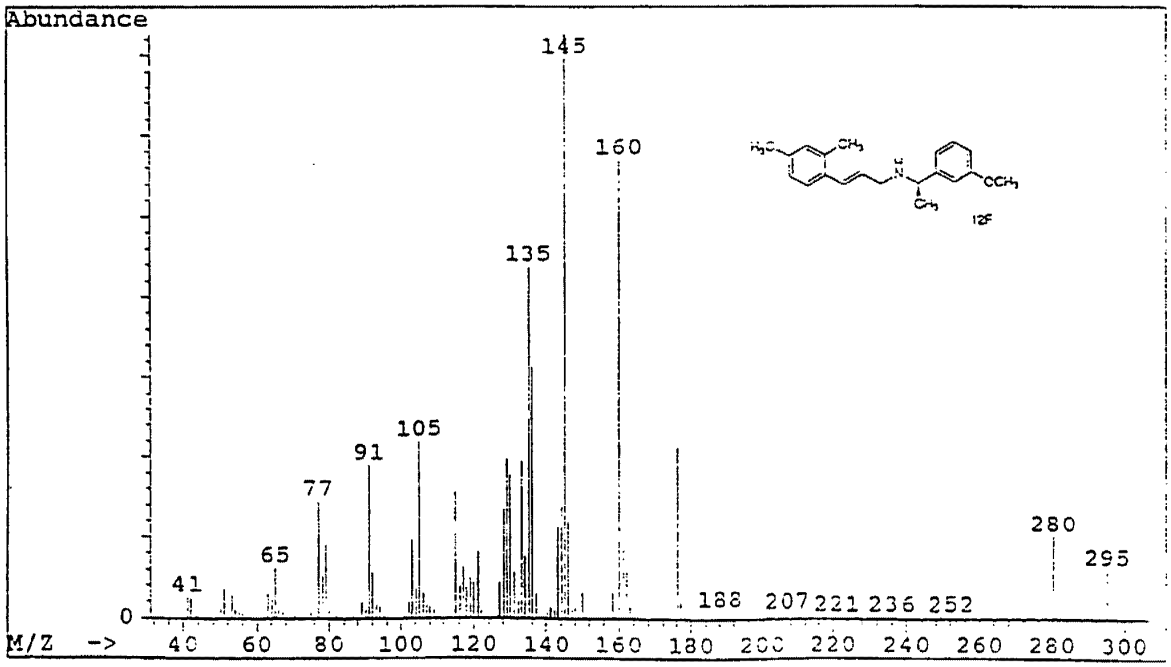


FIGURE 34

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

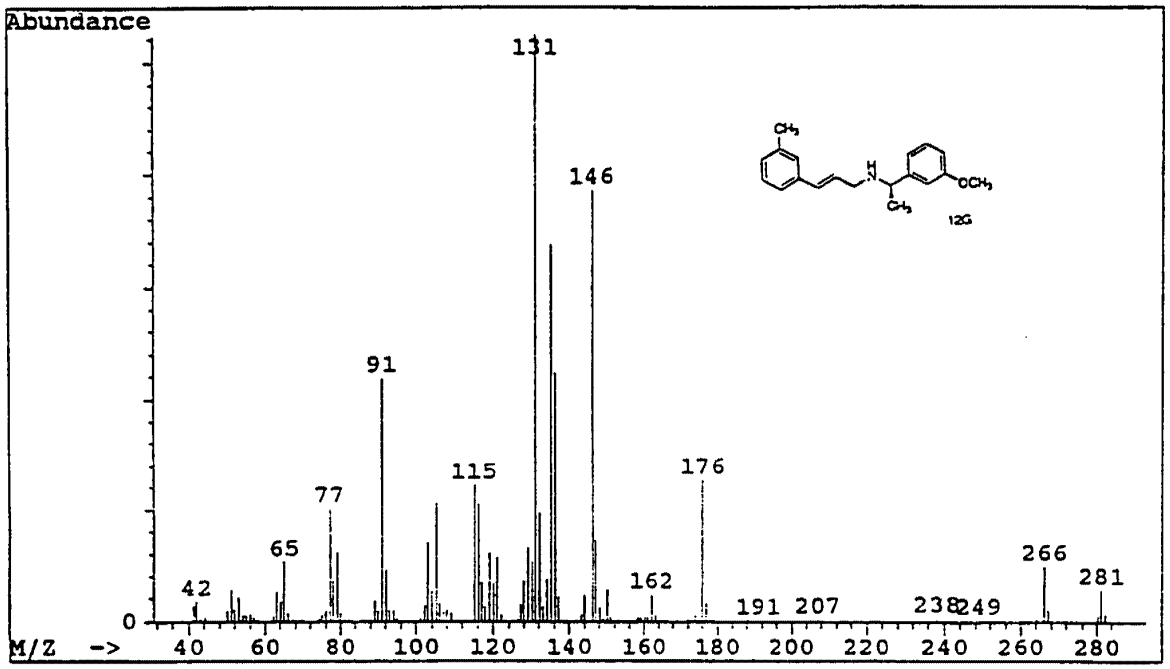


FIGURE 35

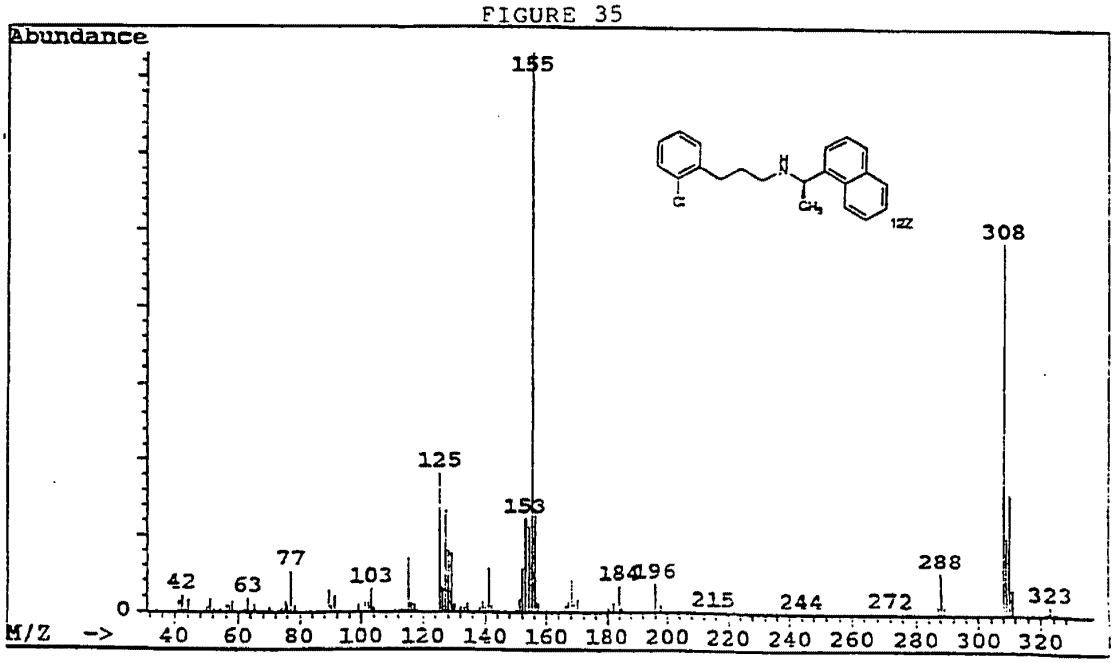


FIGURE 36

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

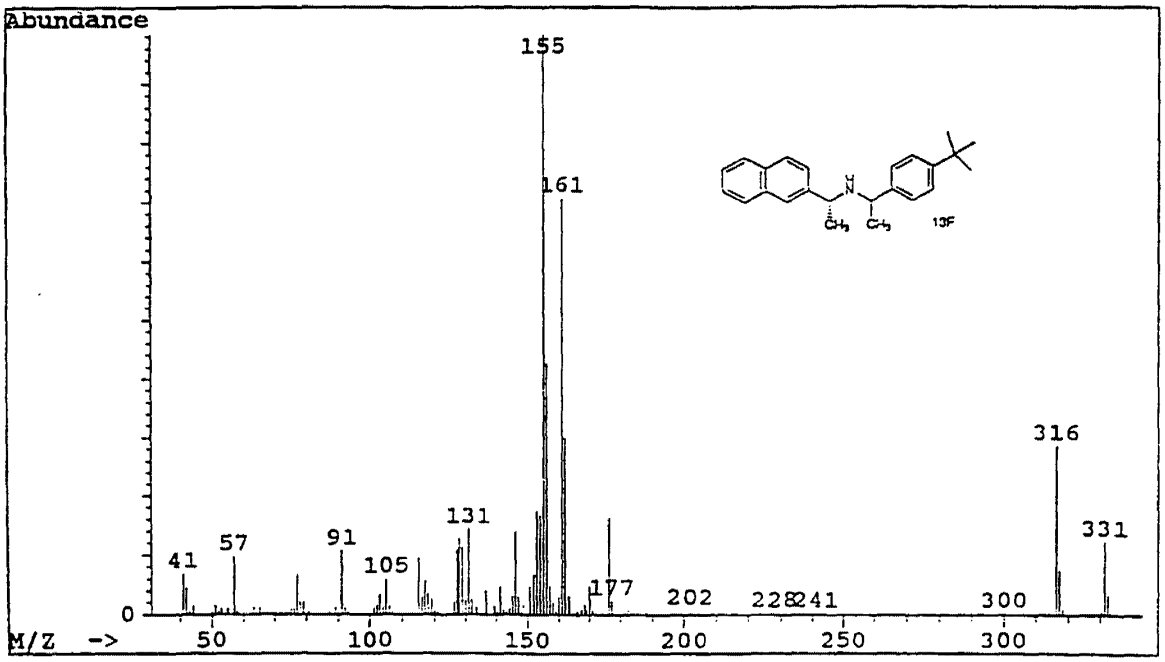


FIGURE 37

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

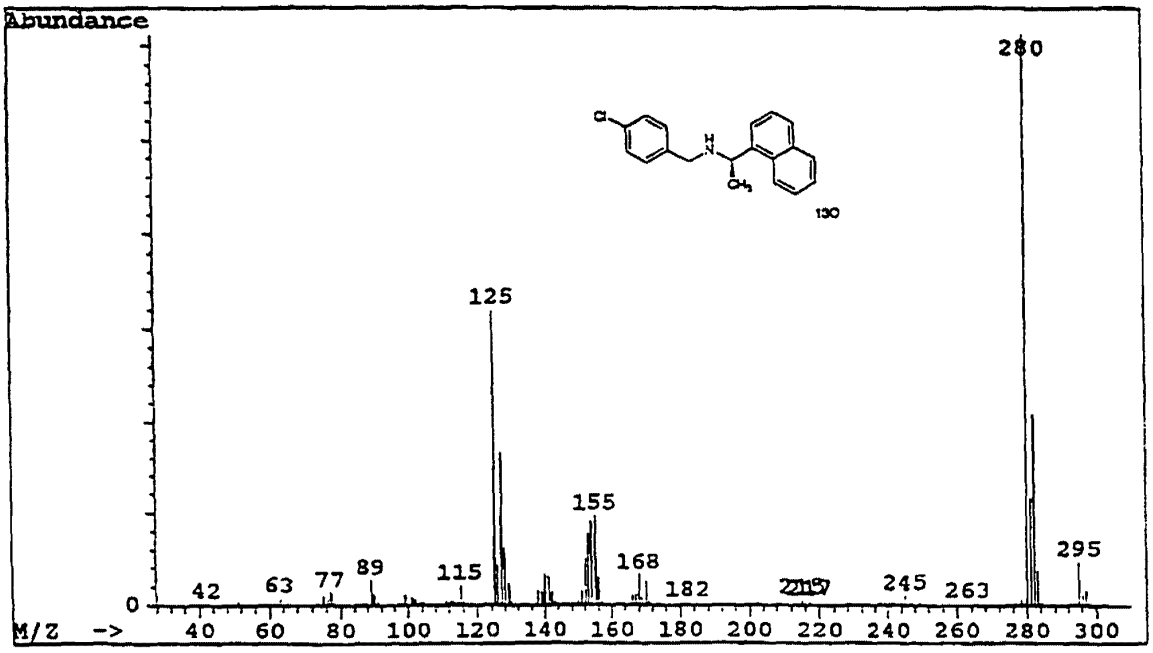


FIGURE 38

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

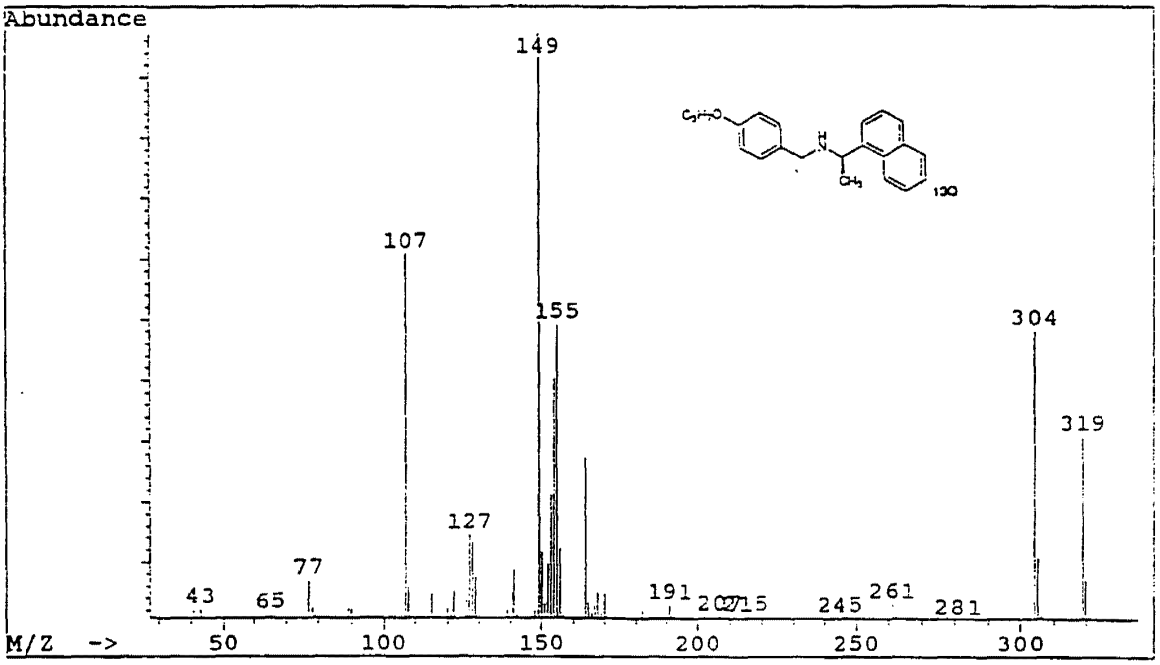


FIGURE 39

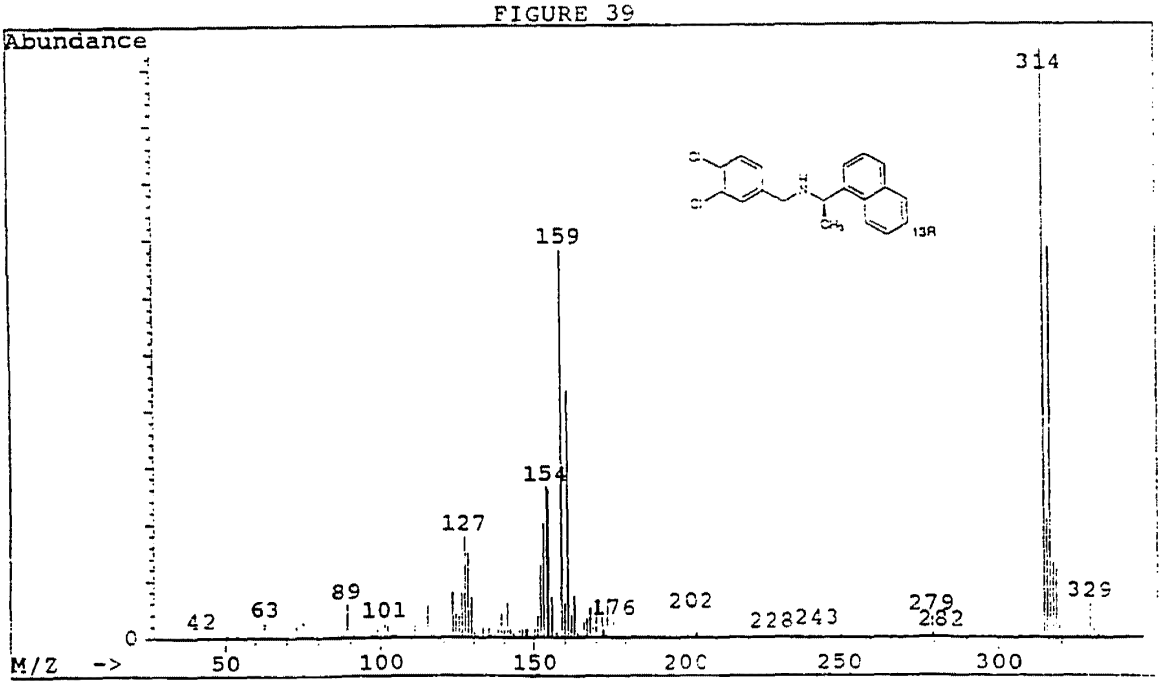


FIGURE 40

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

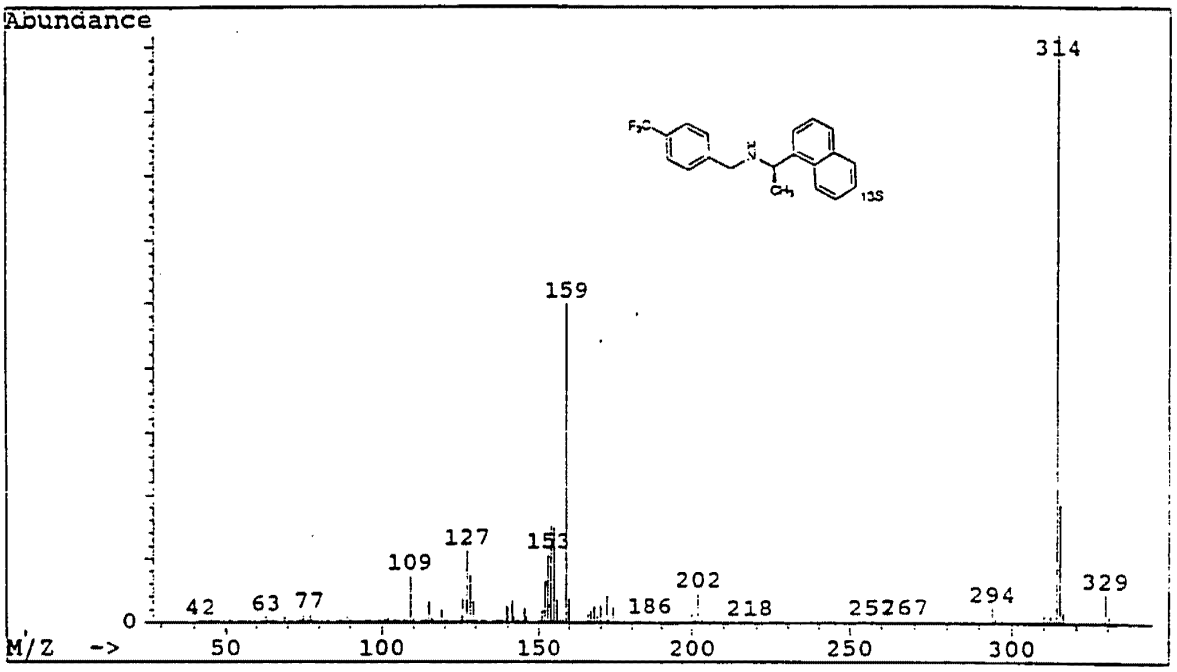


FIGURE 41

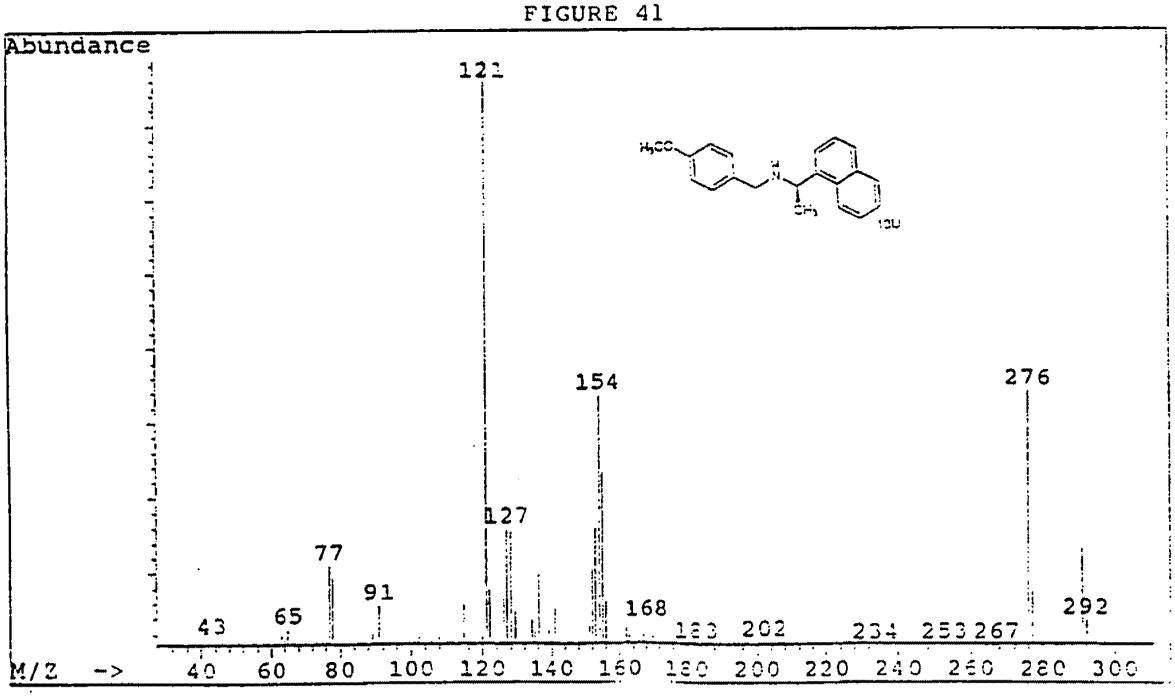


FIGURE 42

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

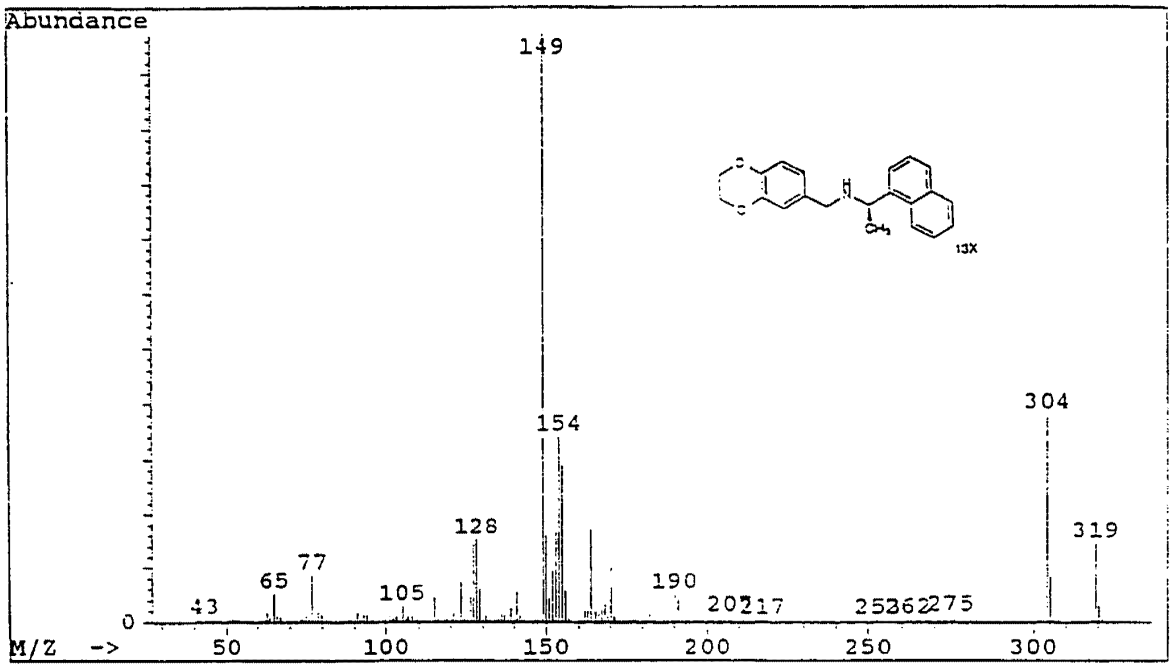


FIGURE 43

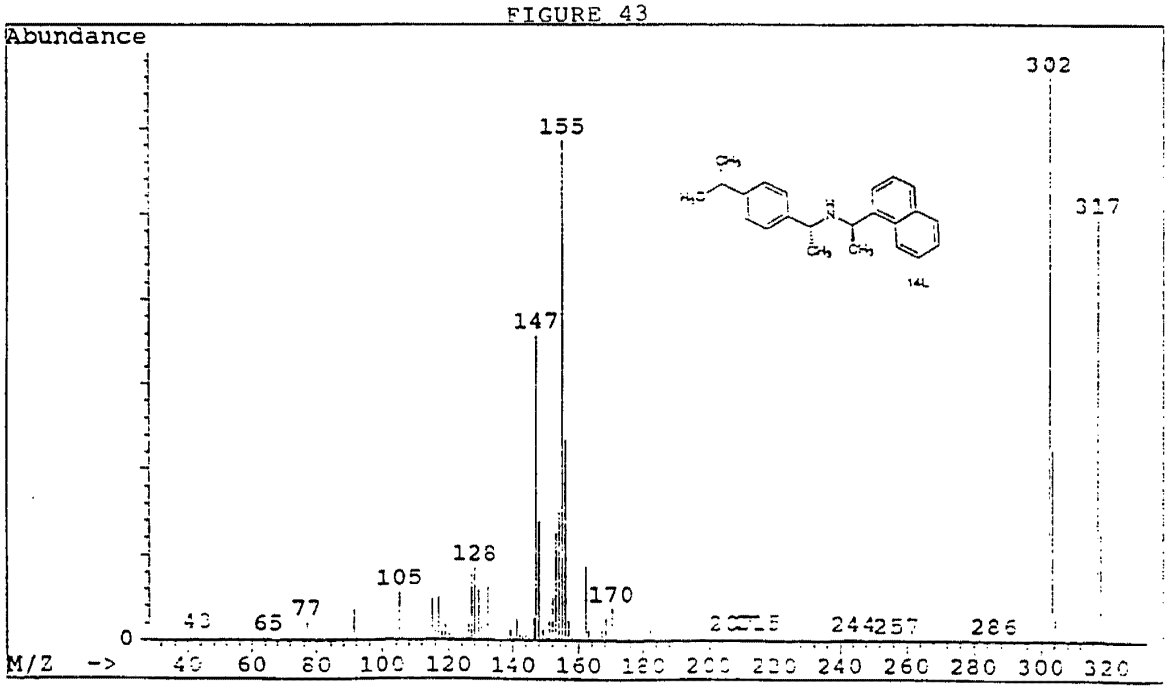


FIGURE 44

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

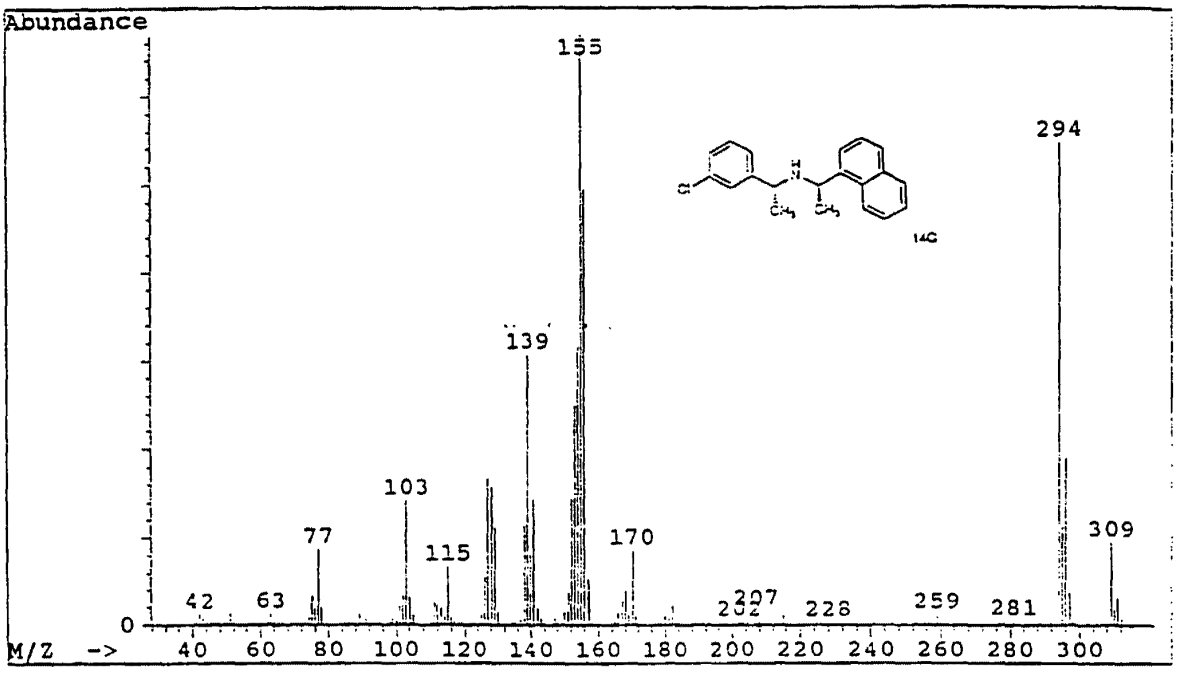


FIGURE 45

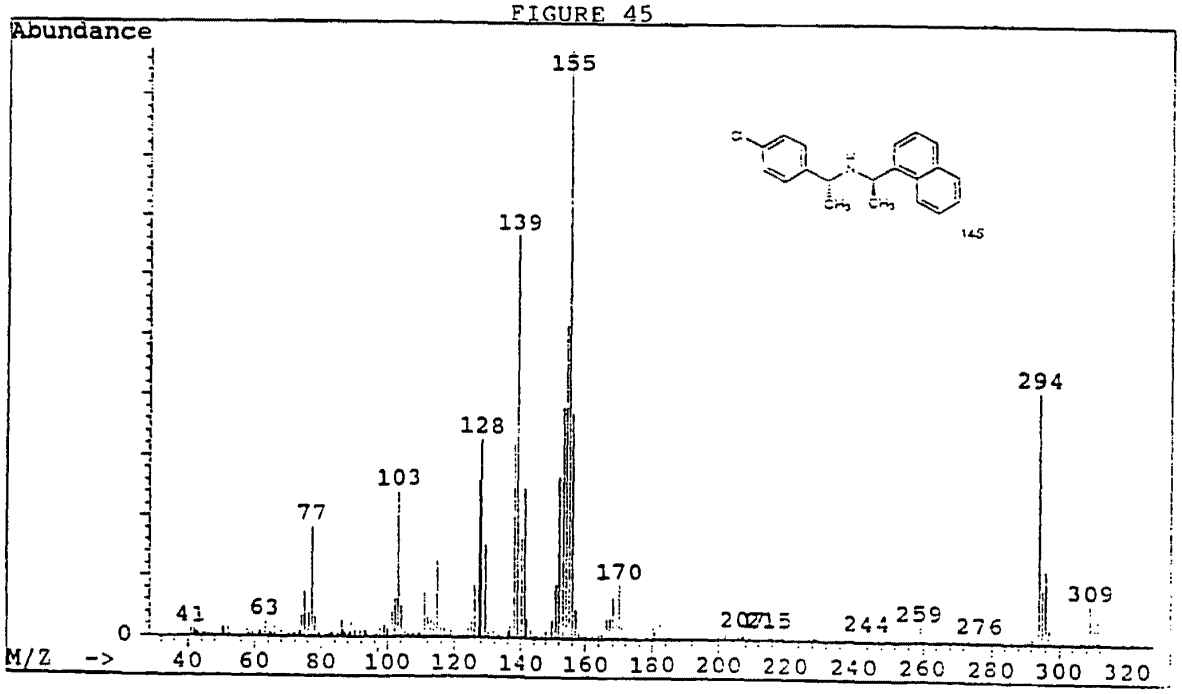


FIGURE 46

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

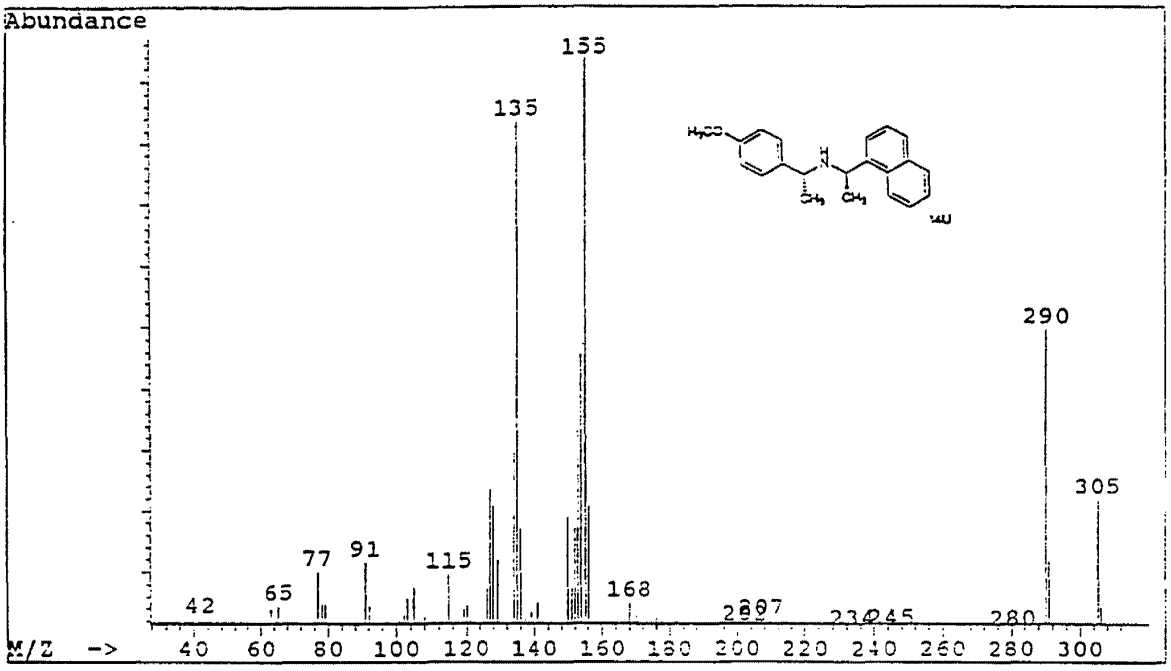


FIGURE 47

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

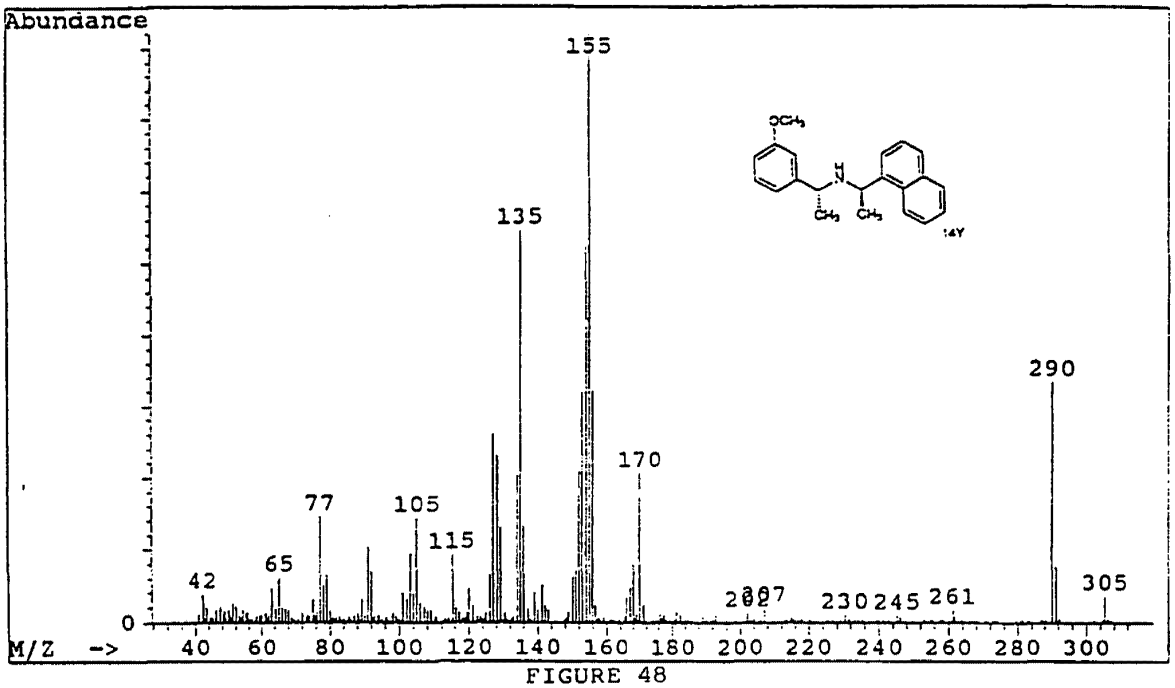


FIGURE 48

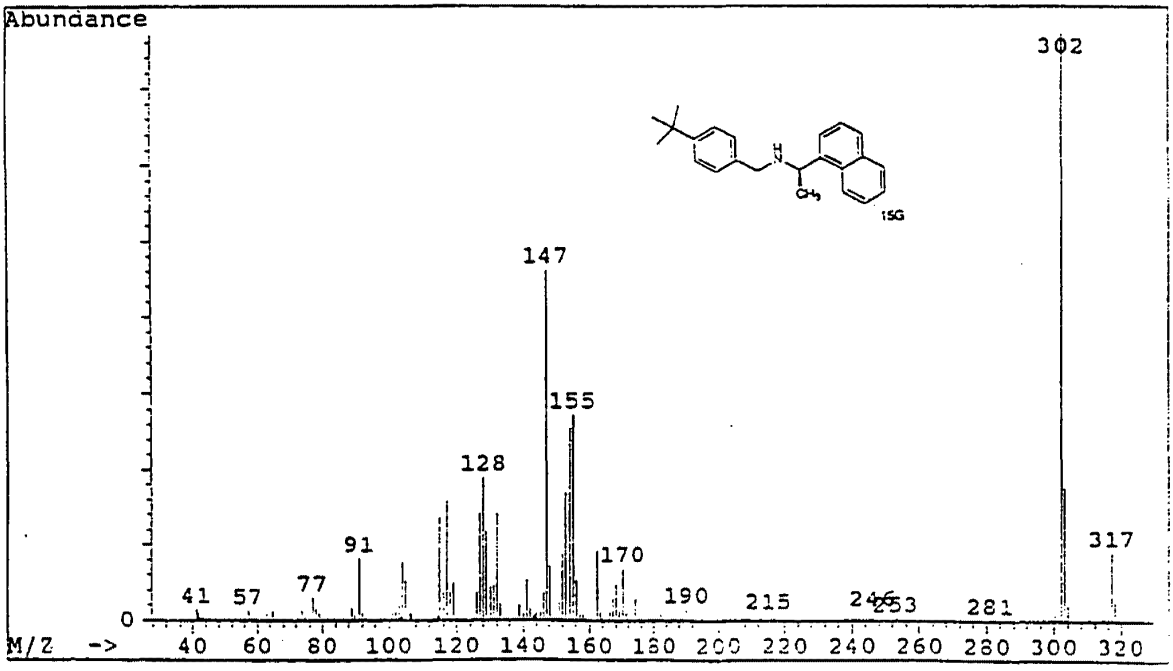


FIGURE 49

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

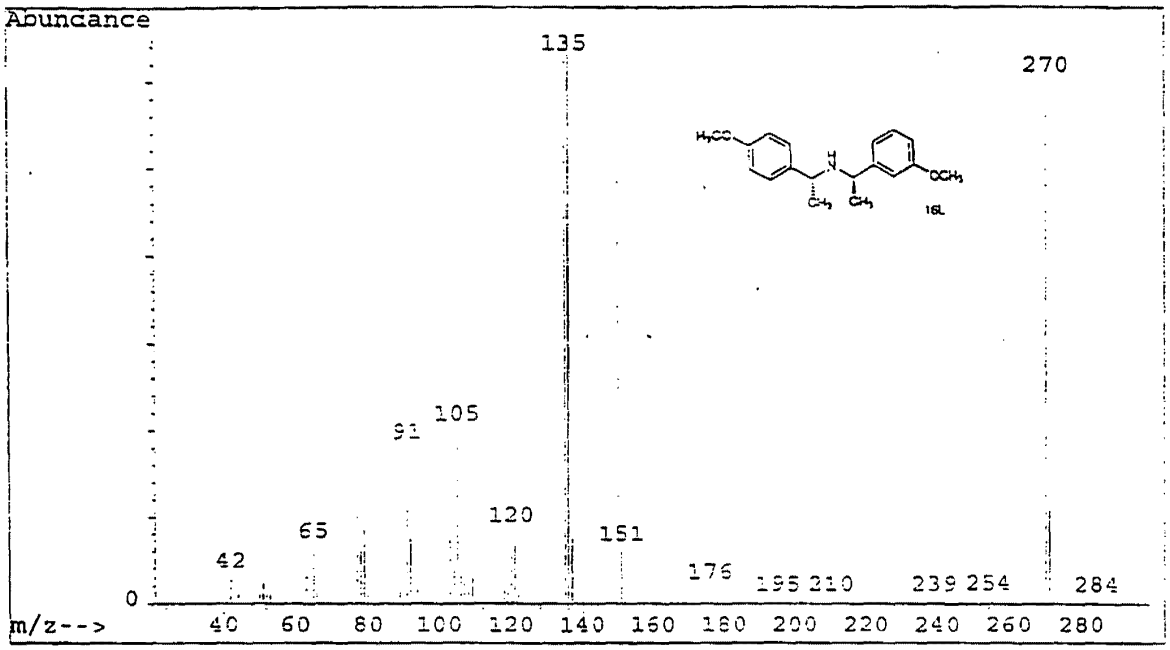


FIGURE 50

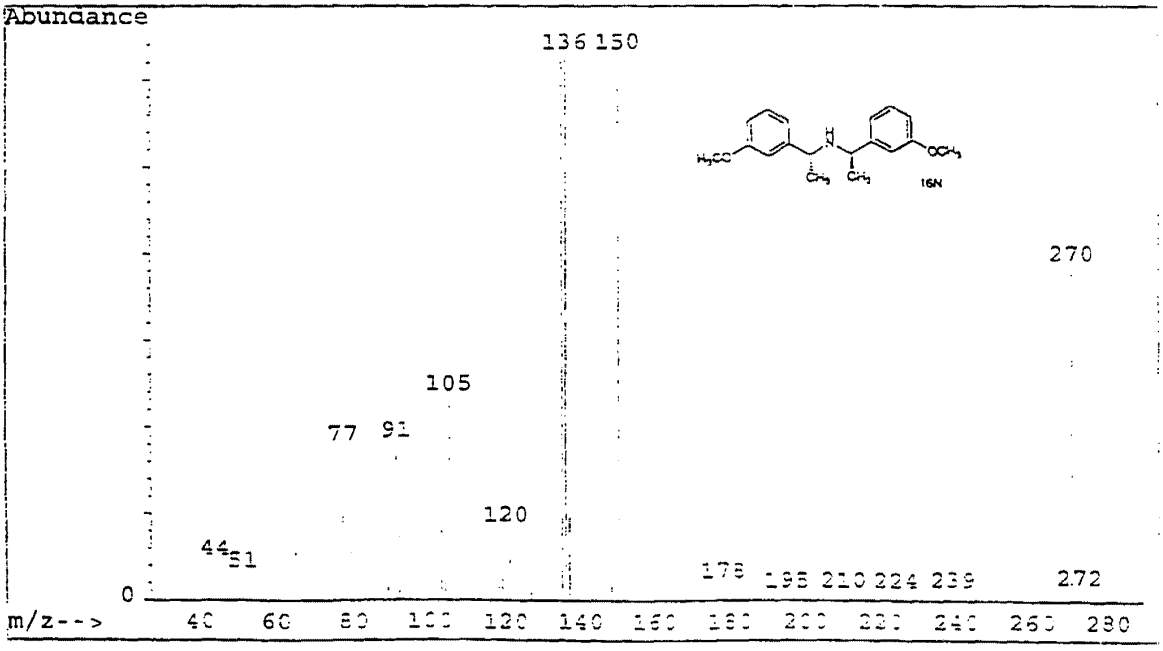


FIGURE 51

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

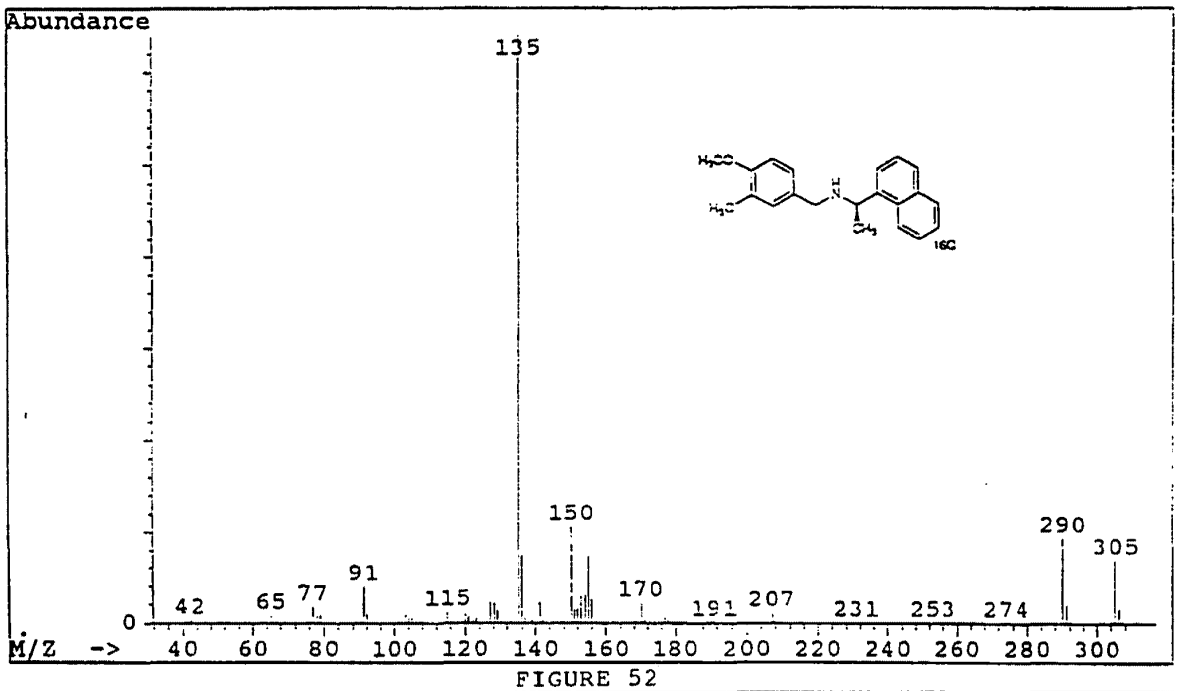


FIGURE 52

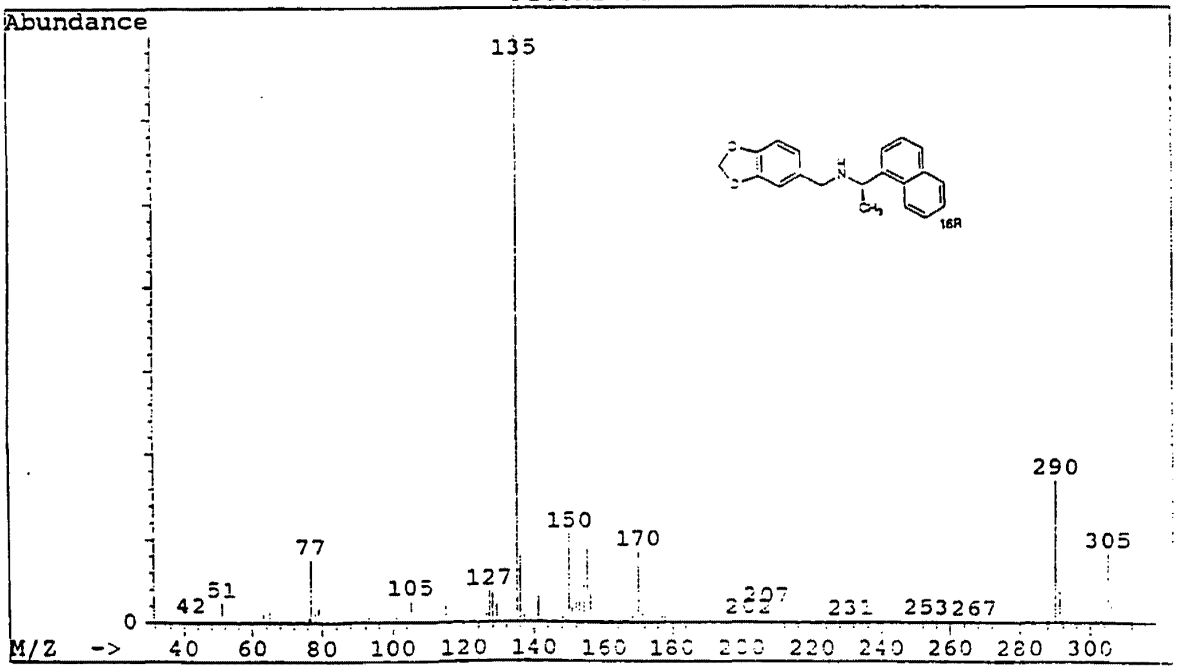


FIGURE 53

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

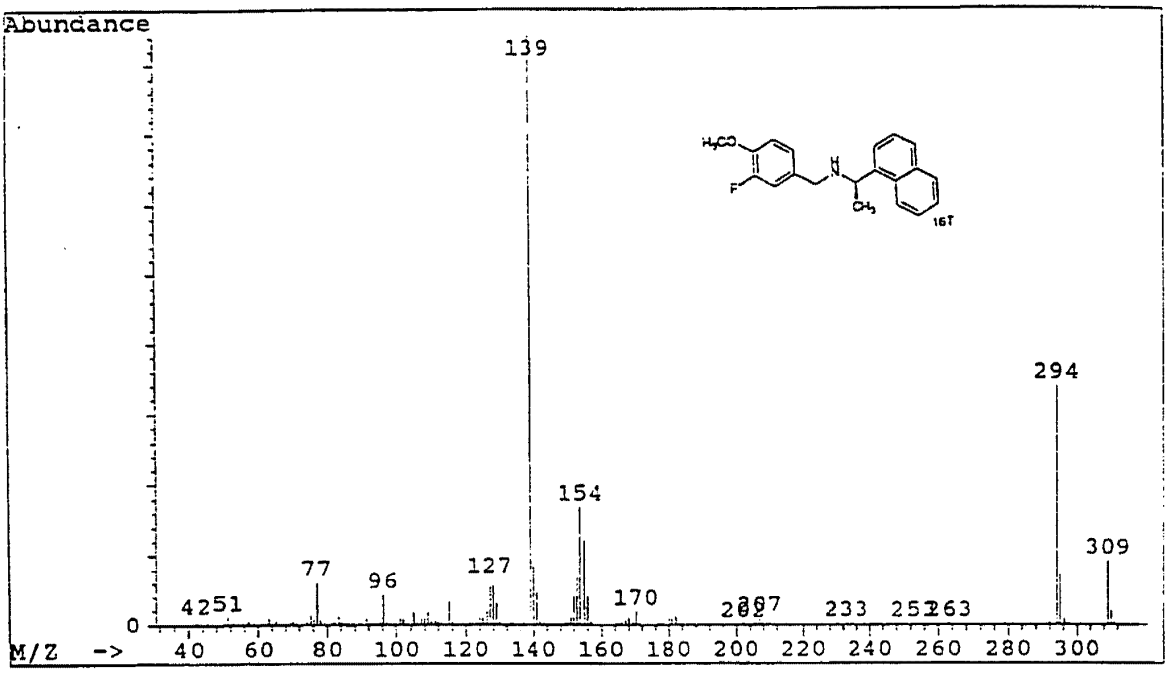


FIGURE 54

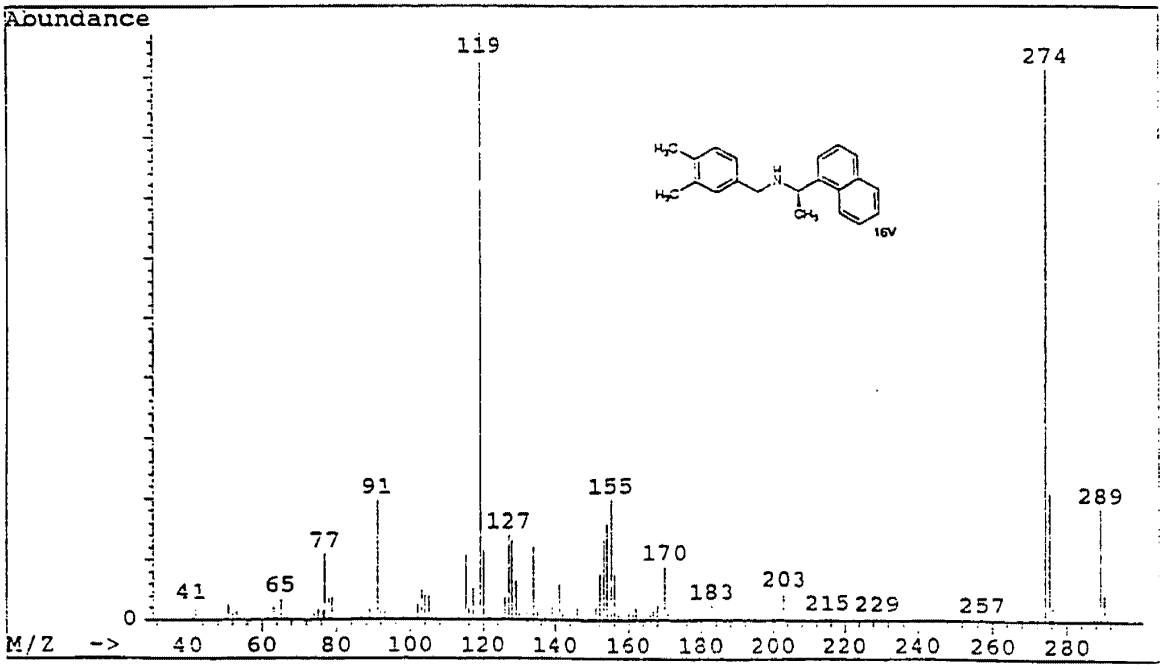


FIGURE 55

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

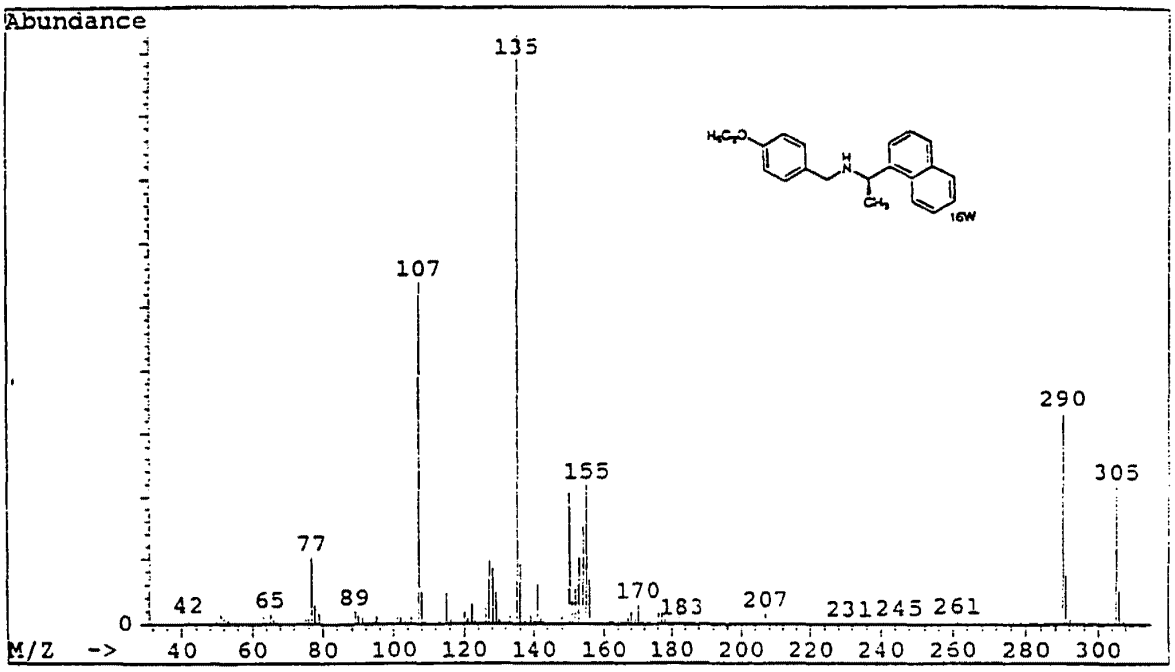


FIGURE 56

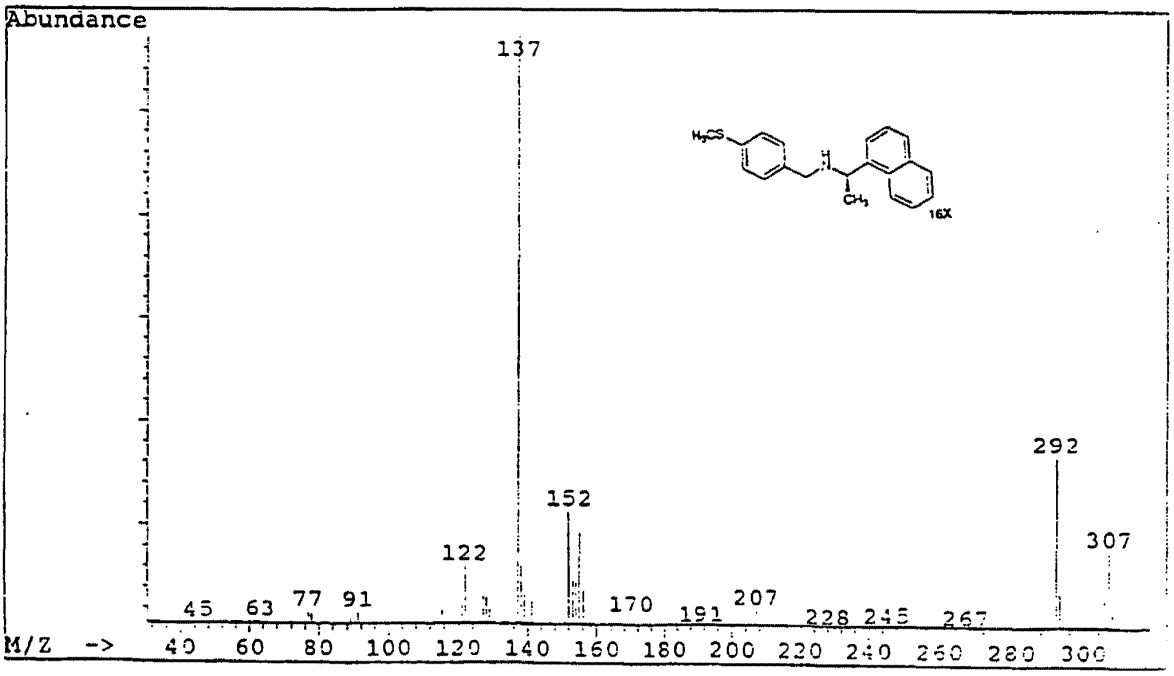


FIGURE 57

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

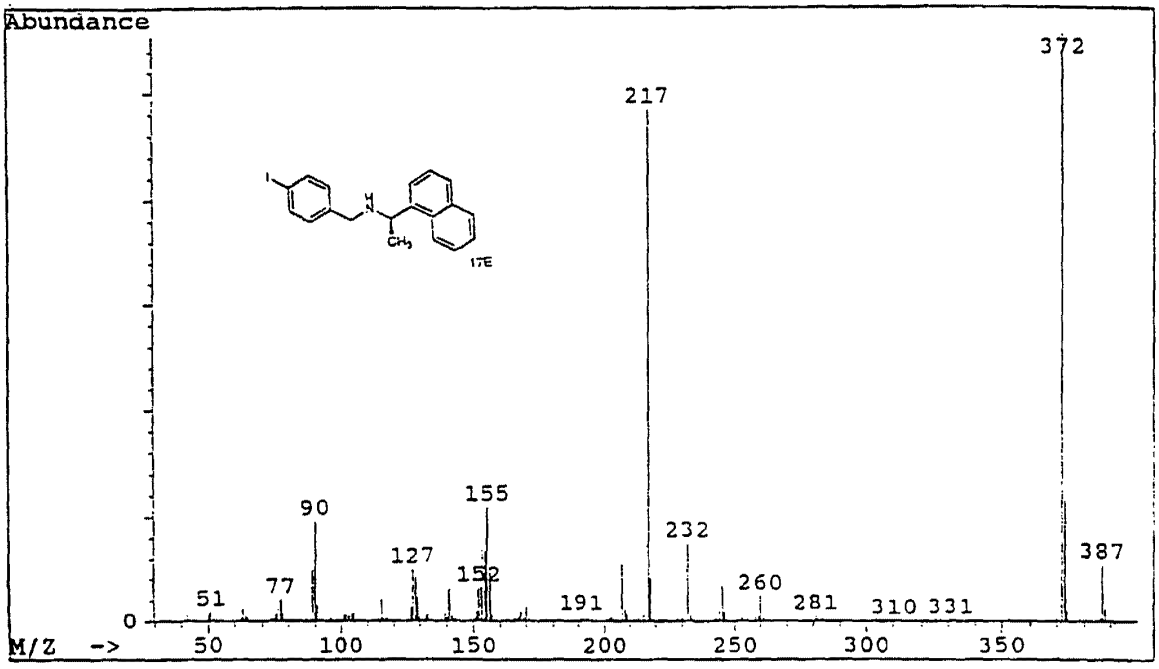


FIGURE 58

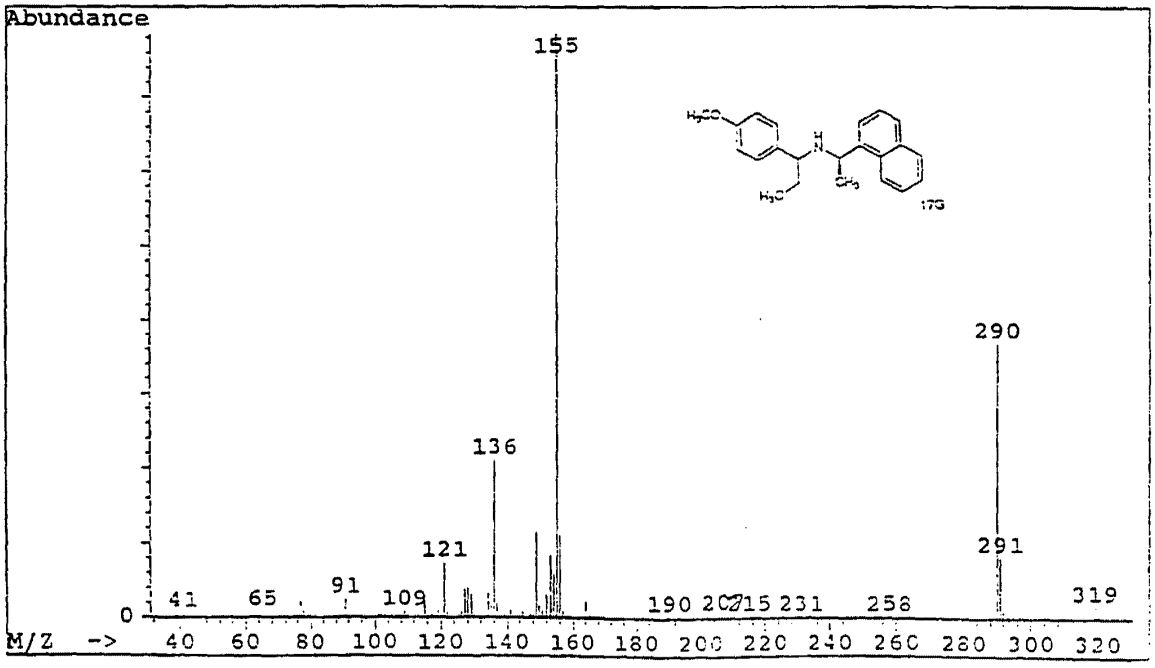


FIGURE 59

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

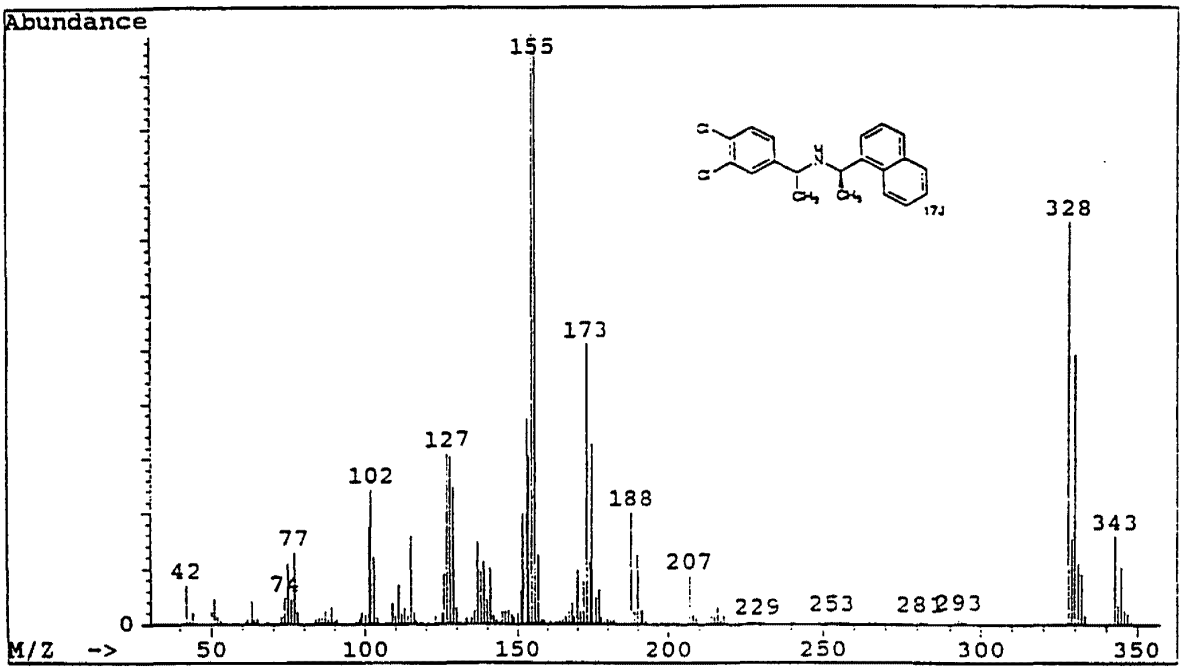


FIGURE 60

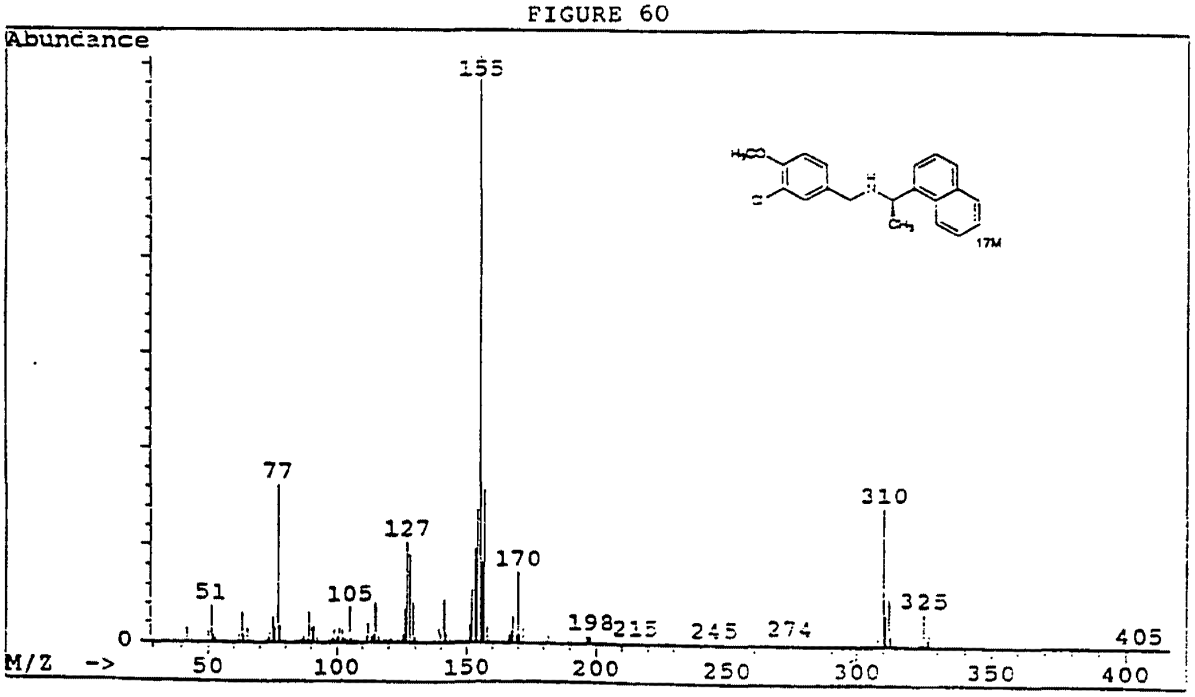


FIGURE 61

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

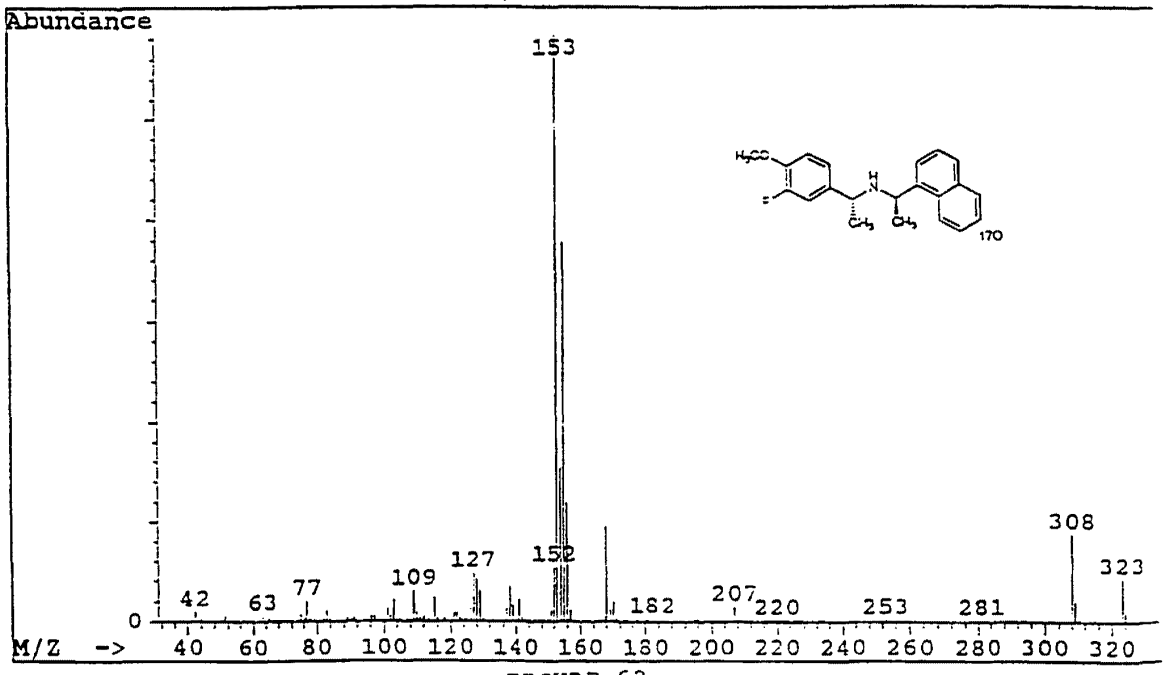


FIGURE 62

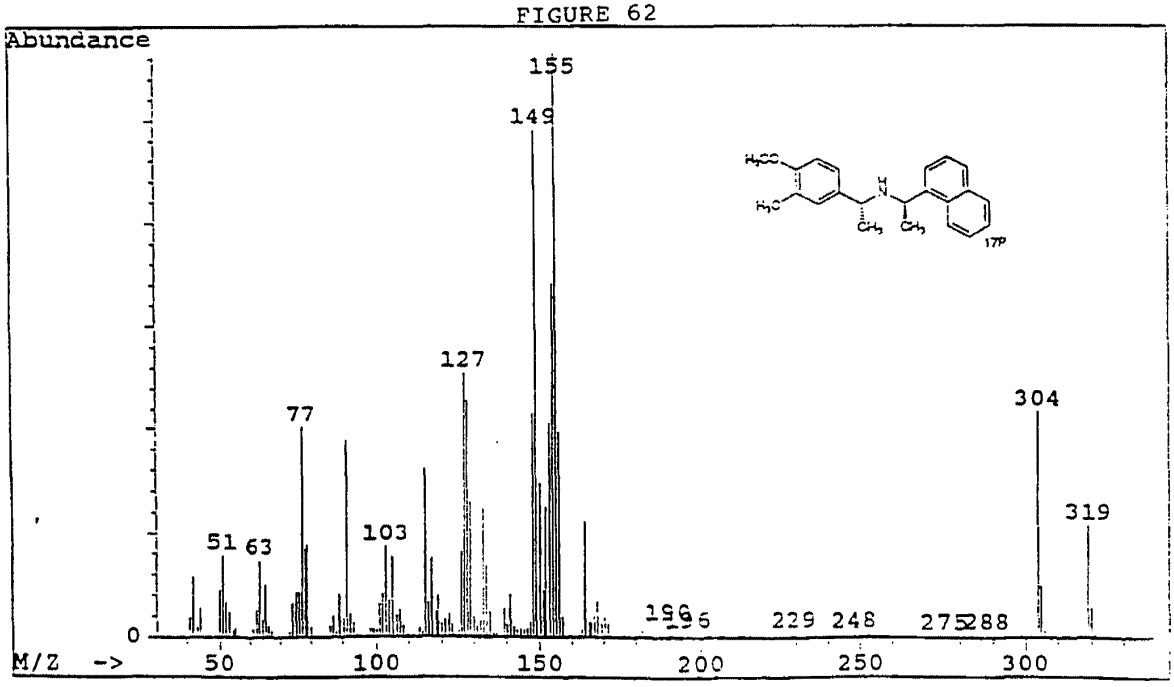


FIGURE 63

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

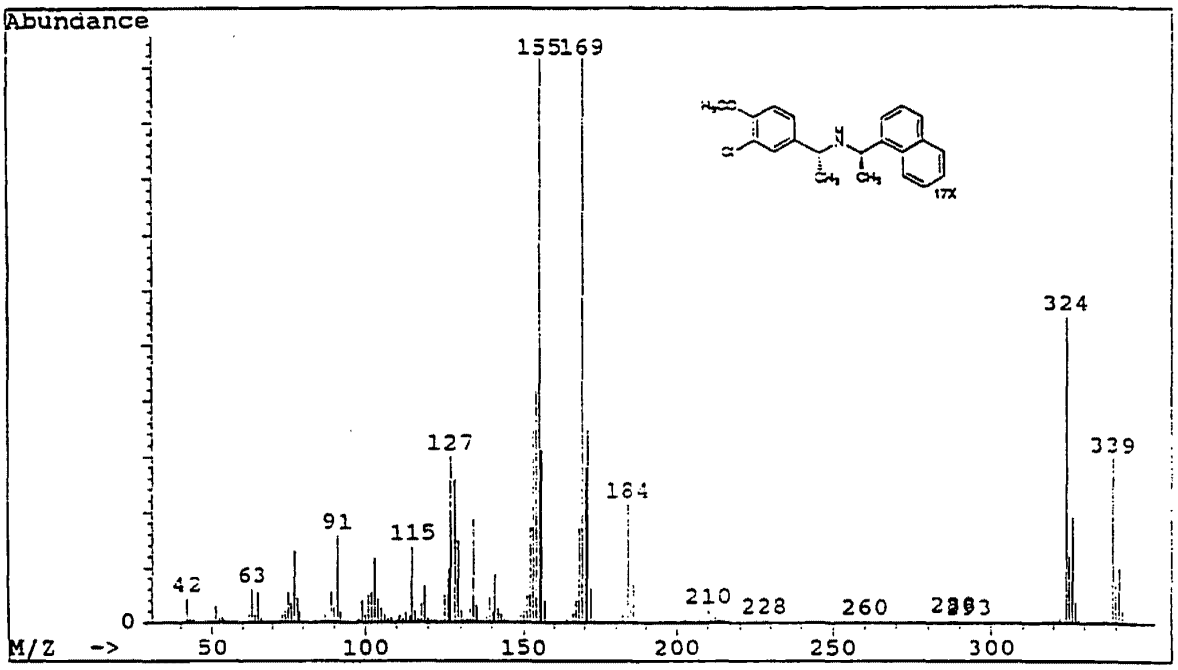


FIGURE 64

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

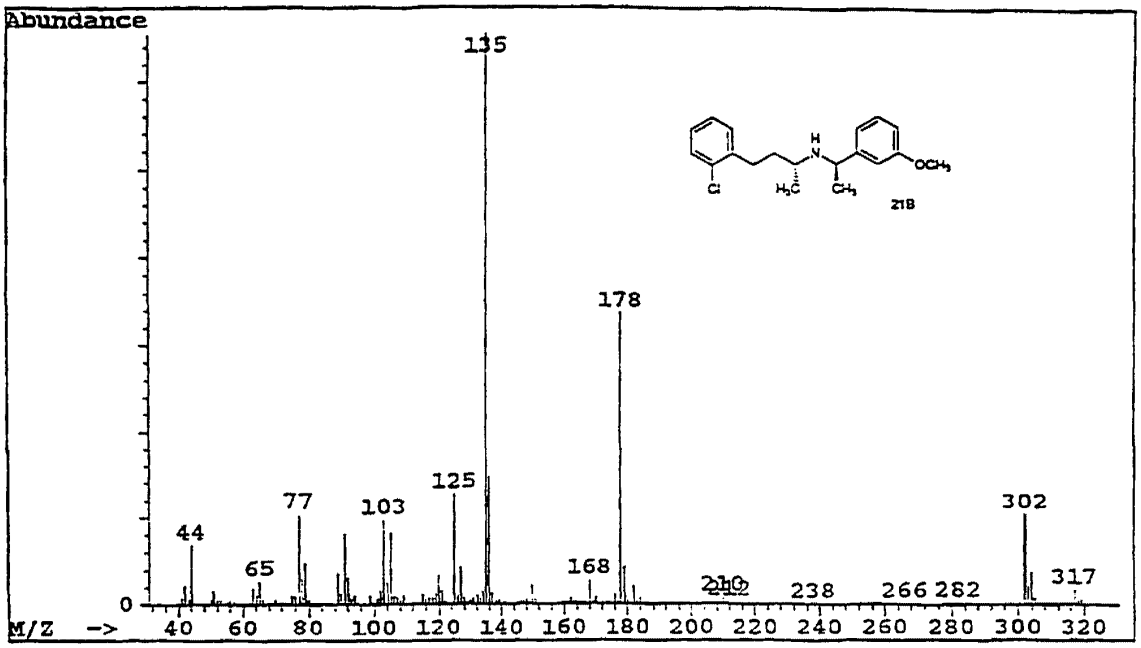
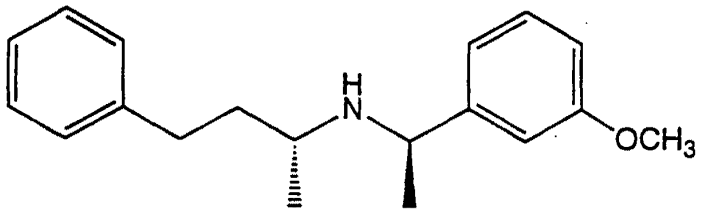


FIGURE 65

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



21D

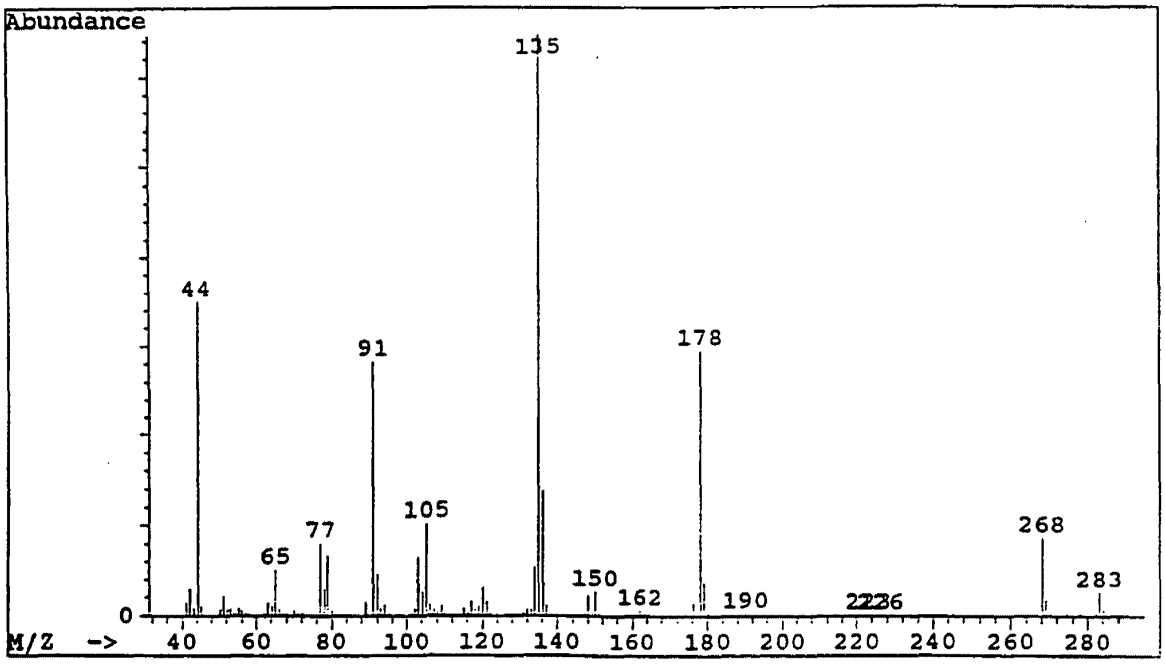
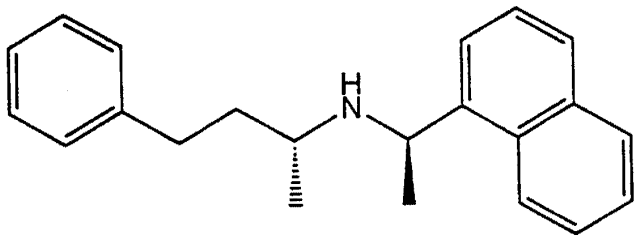


FIGURE 66

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



21F

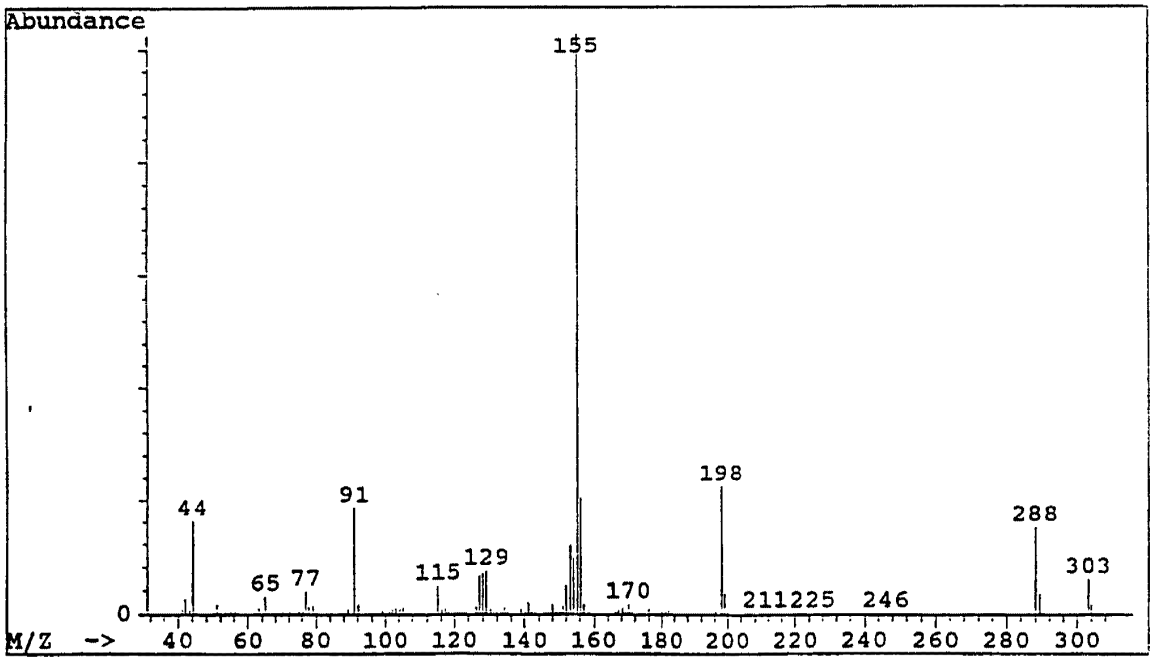
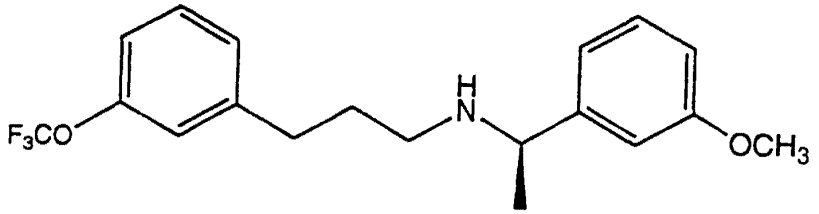


FIGURE 67

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



21M

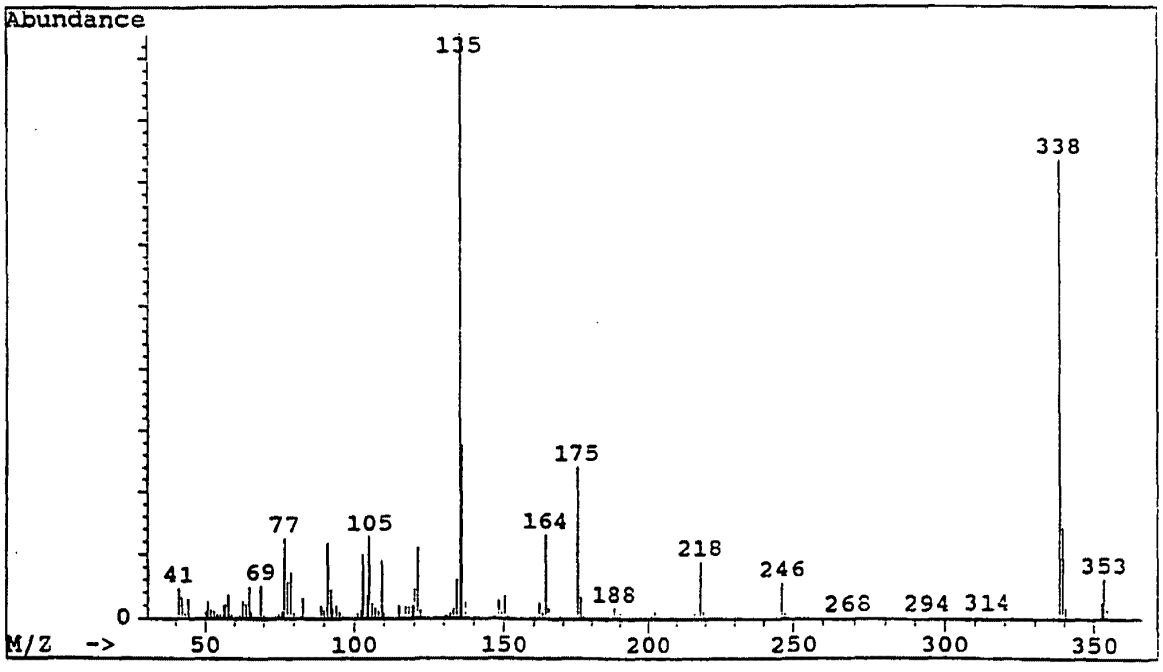


FIGURE 68

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

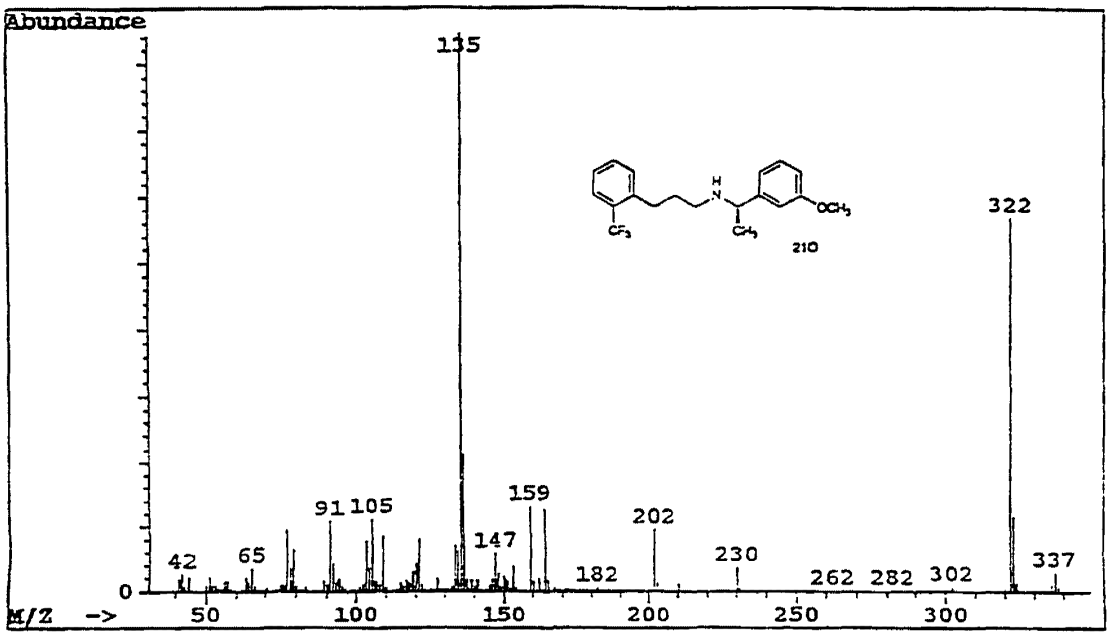


FIGURE 69

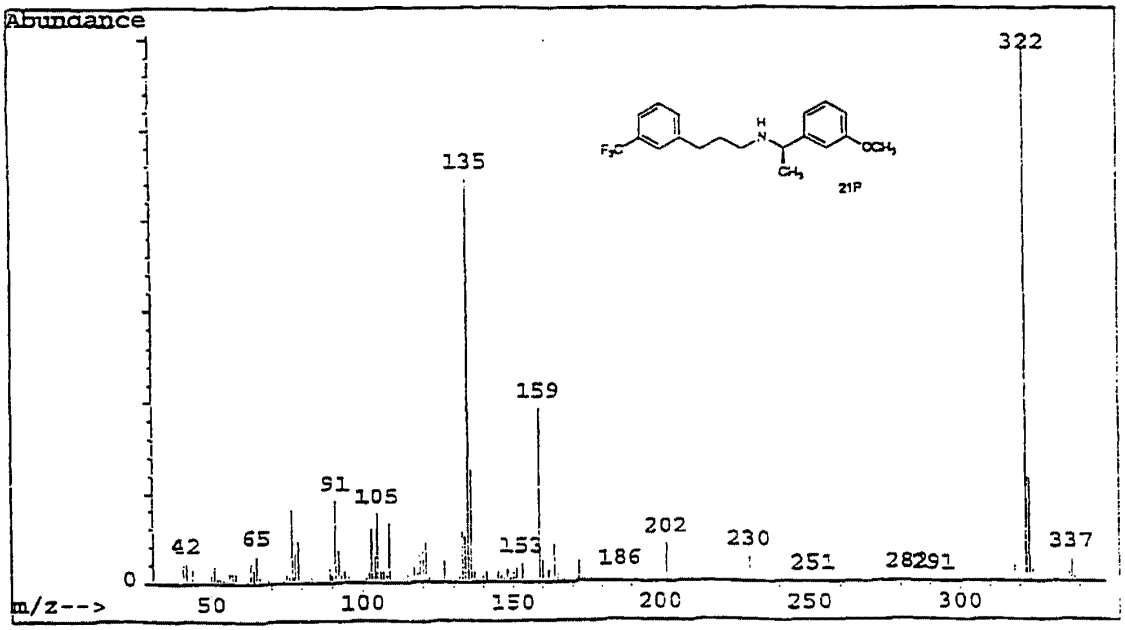


FIGURE 70

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

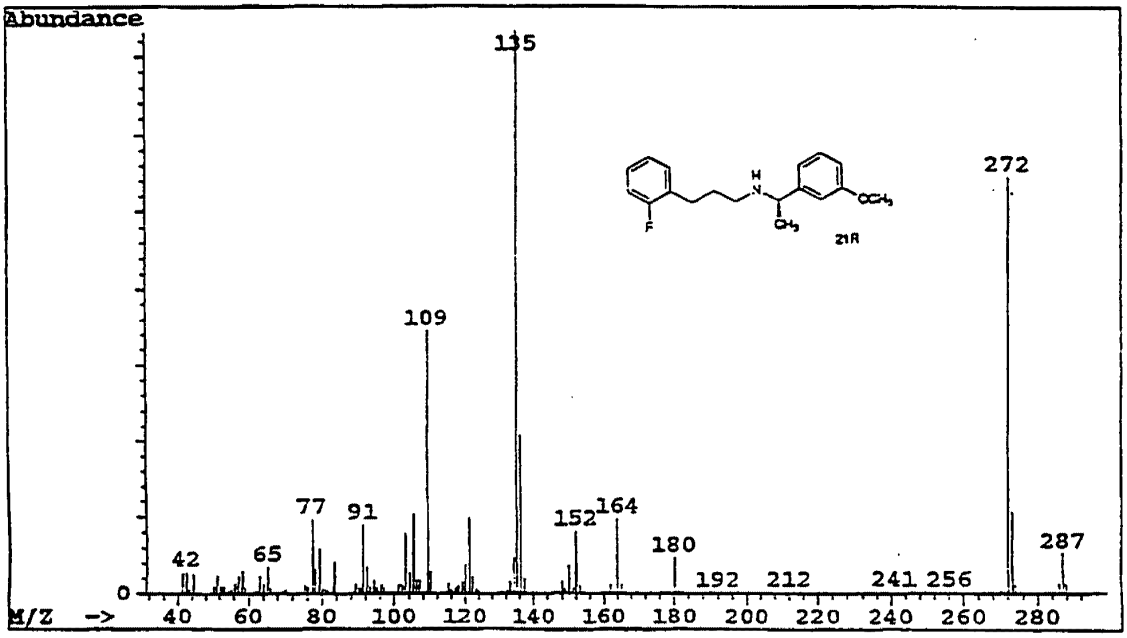
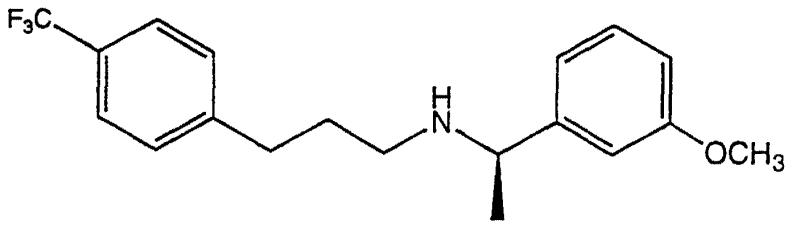


FIGURE 71

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



21Q

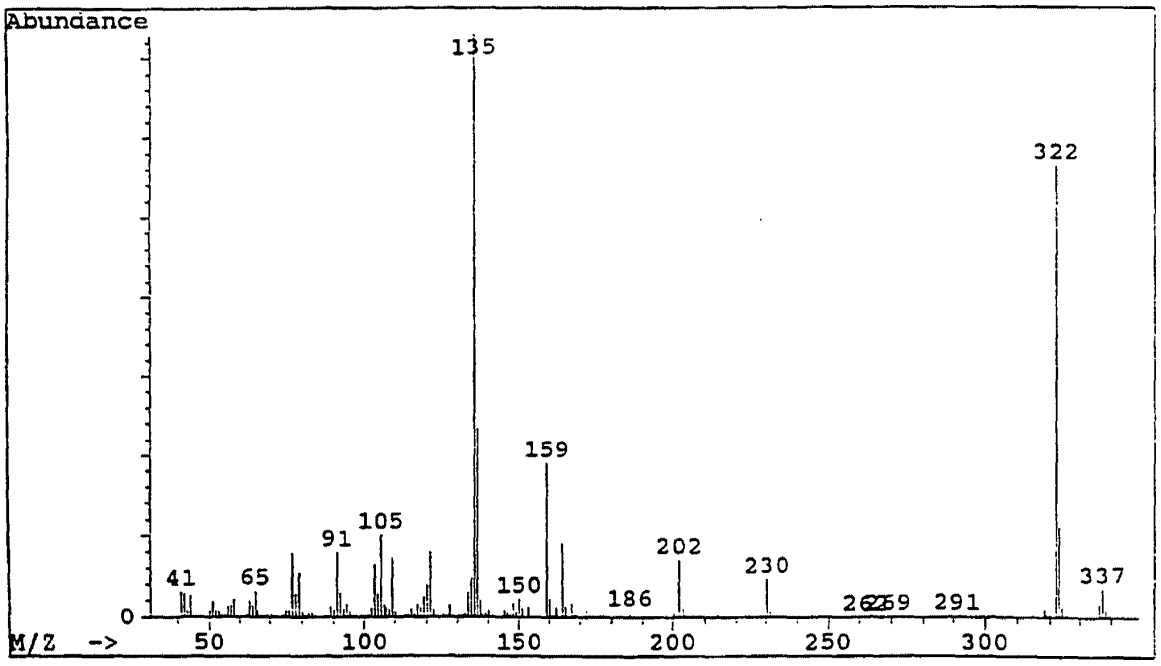
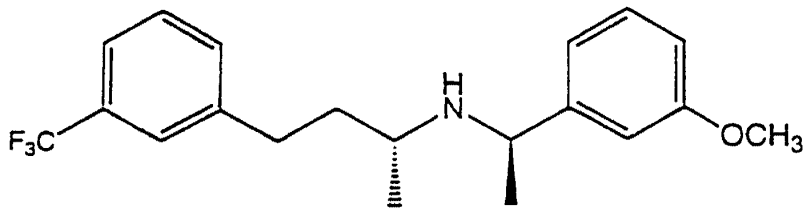


FIGURE 72

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



21Y

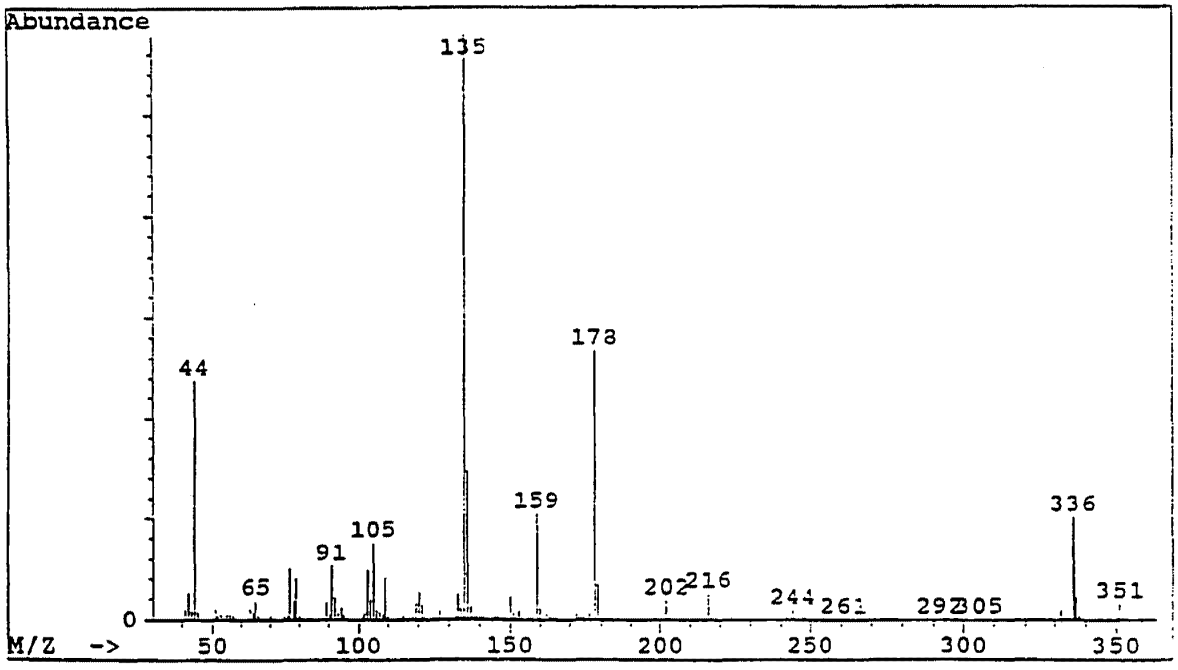
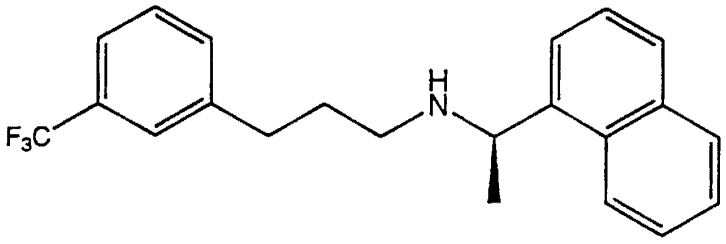


FIGURE 73

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



22J

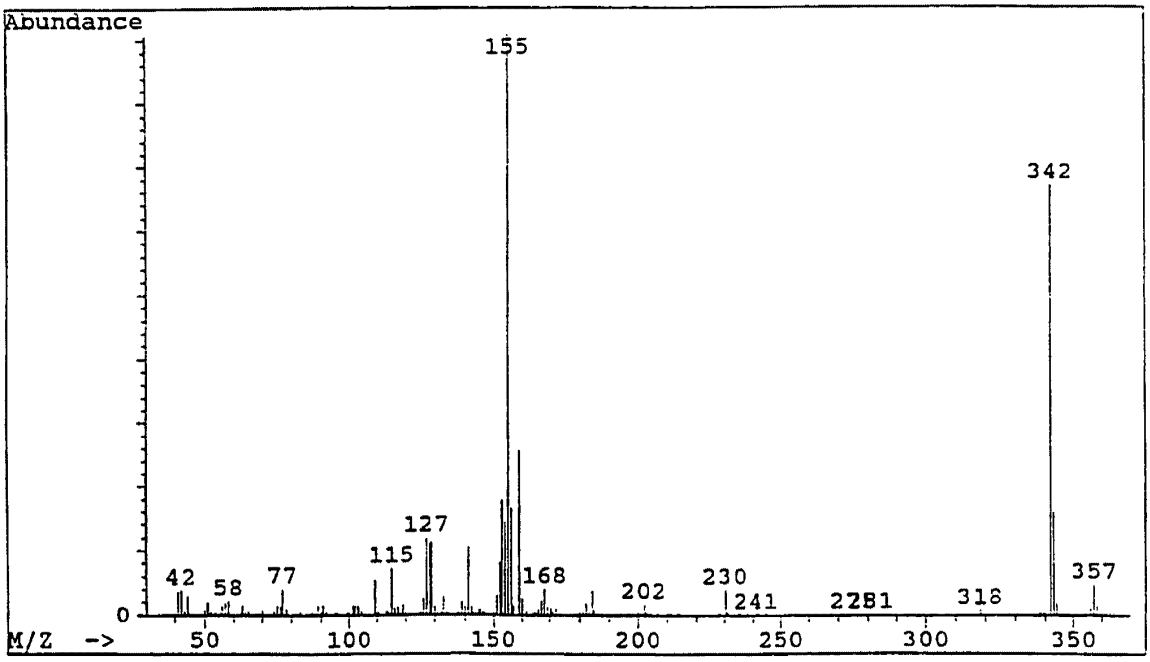
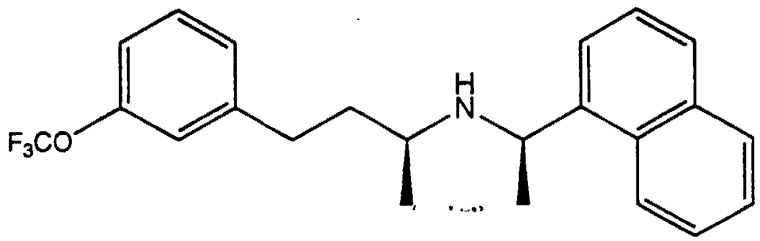


FIGURE 74

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



22X

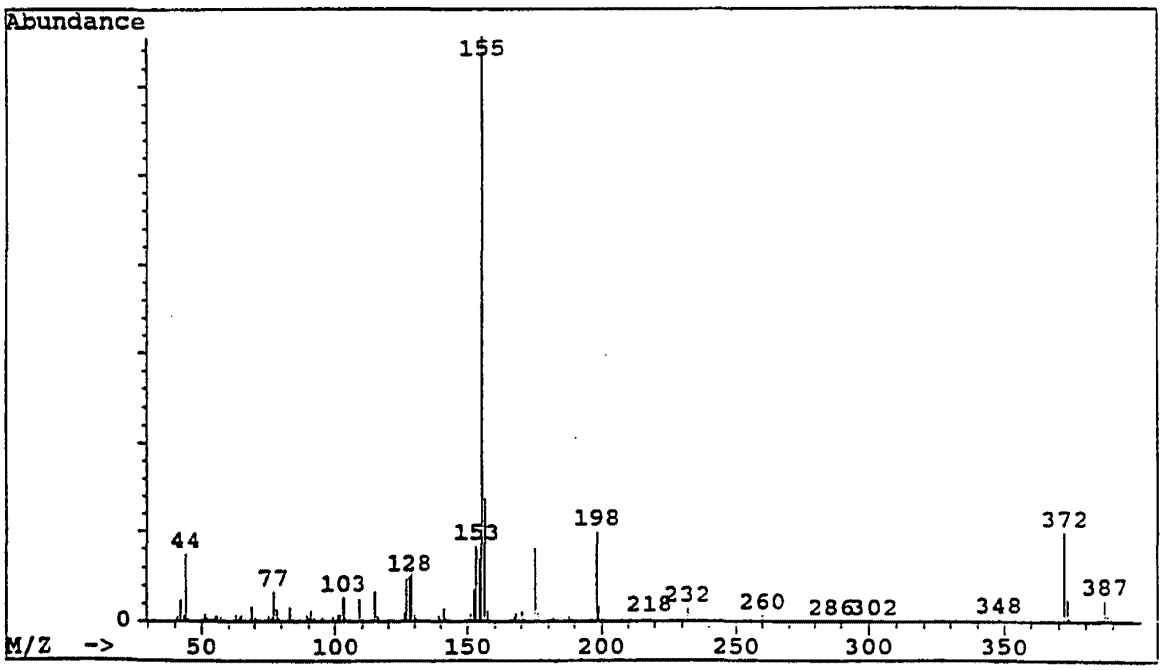
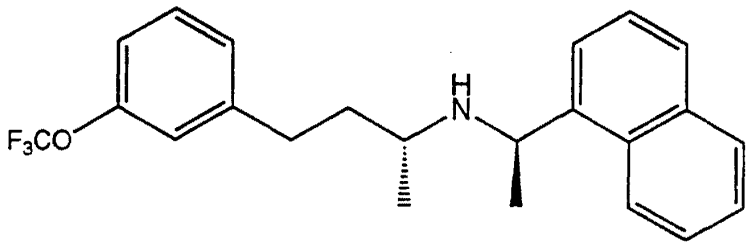


FIGURE 75

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



22Y

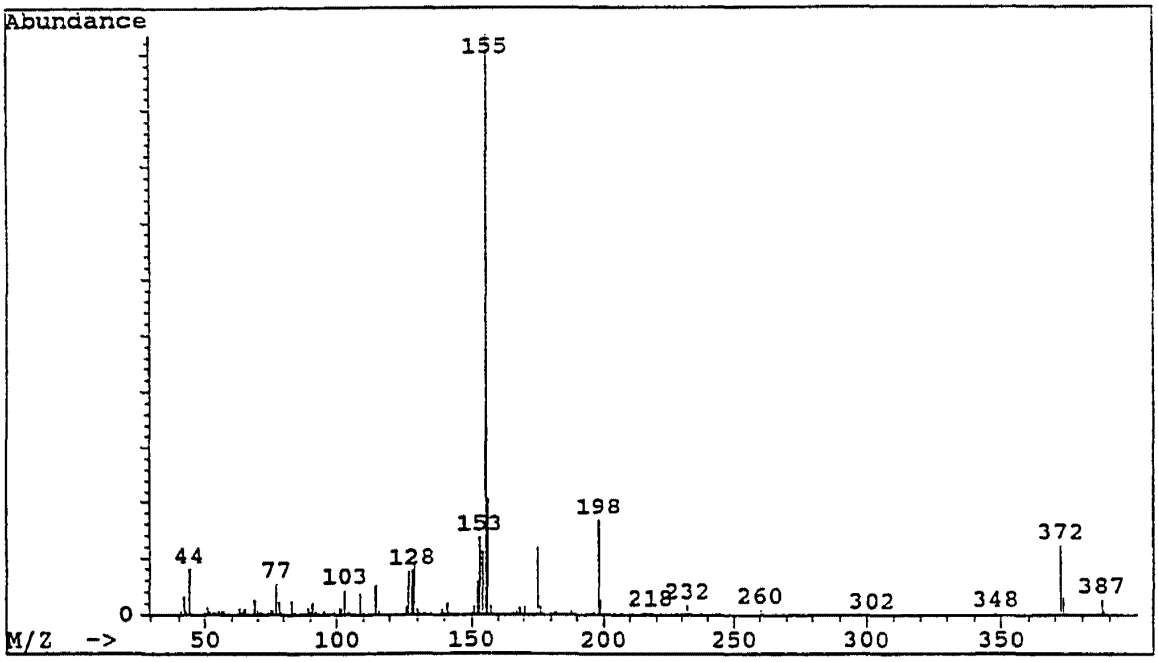
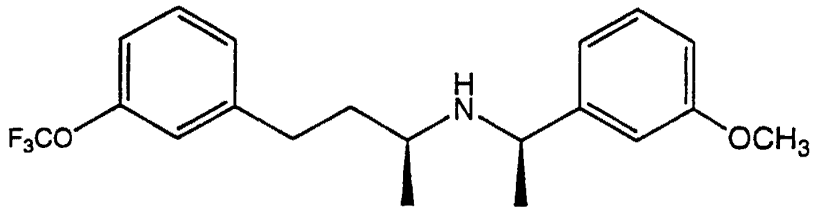


FIGURE 76

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



22Z

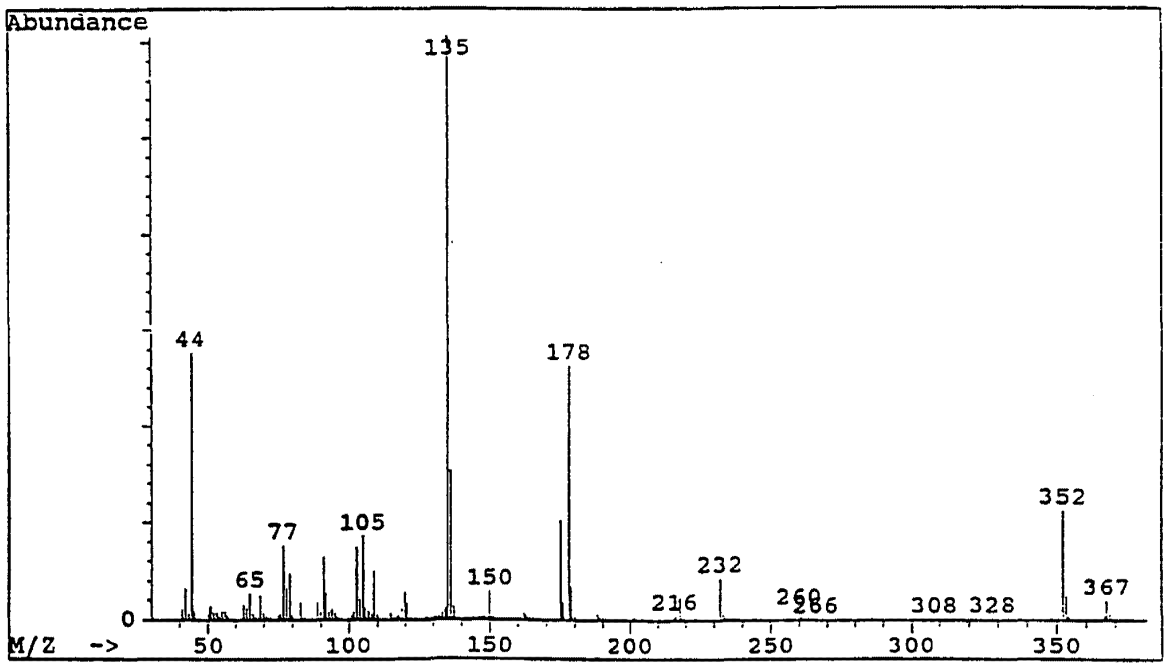
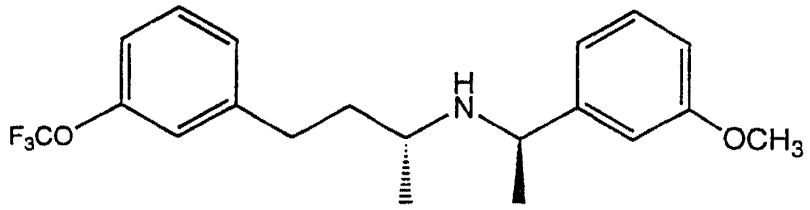


FIGURE 77

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



23A

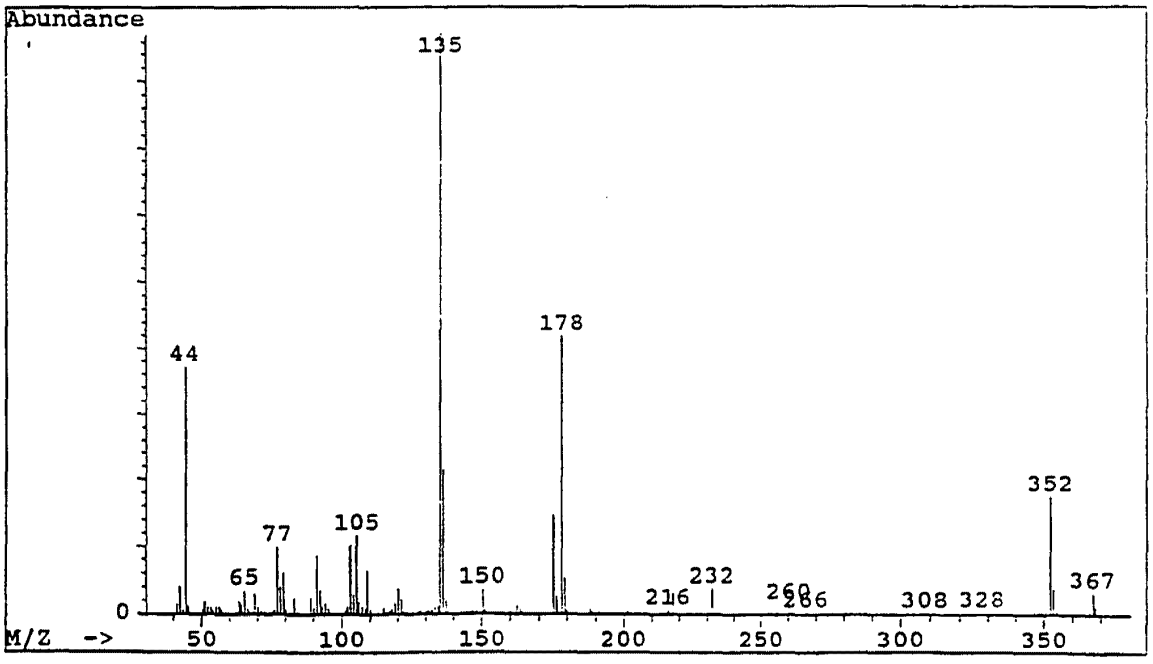
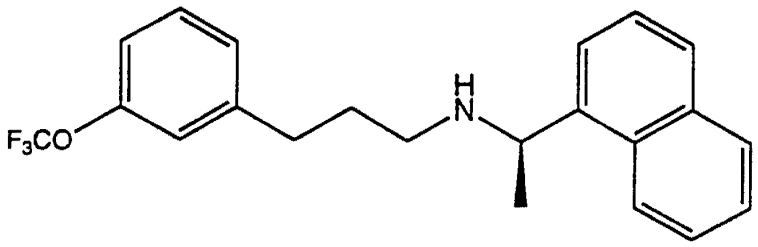


FIGURE 78

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



24J

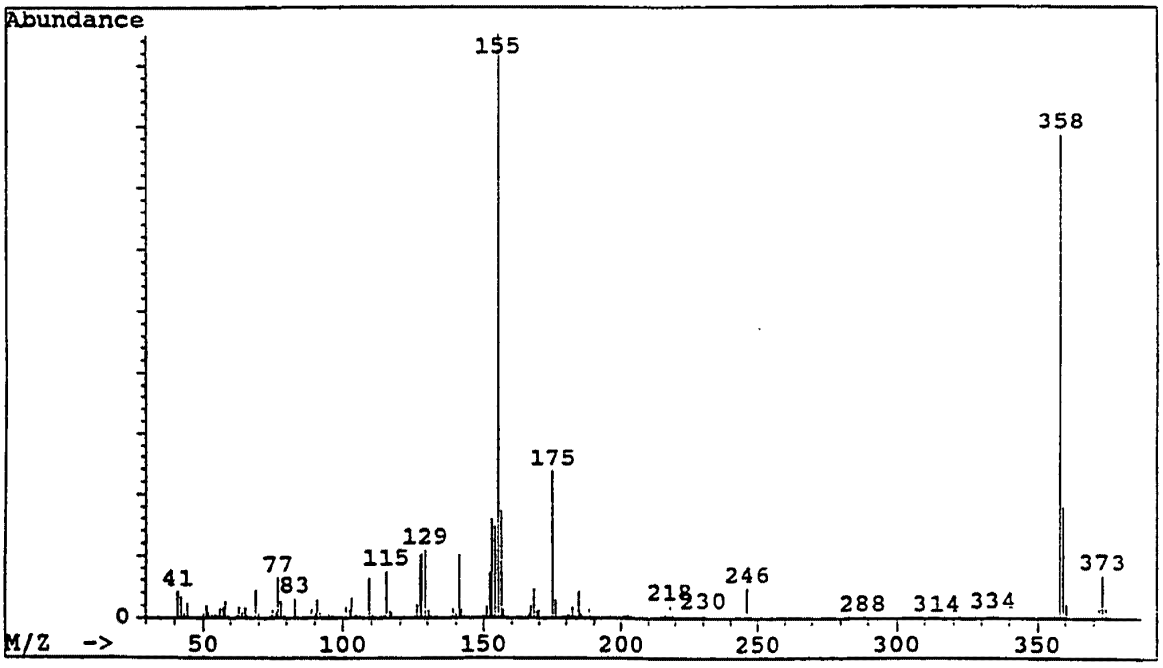
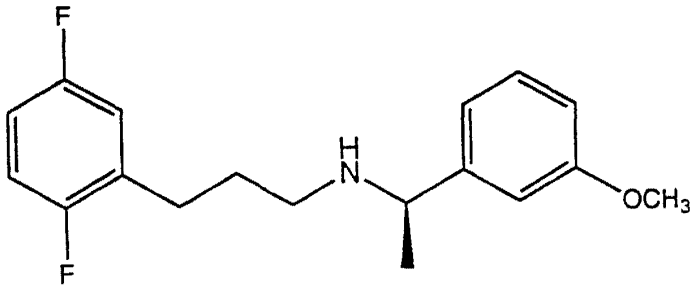


FIGURE 79

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



24K

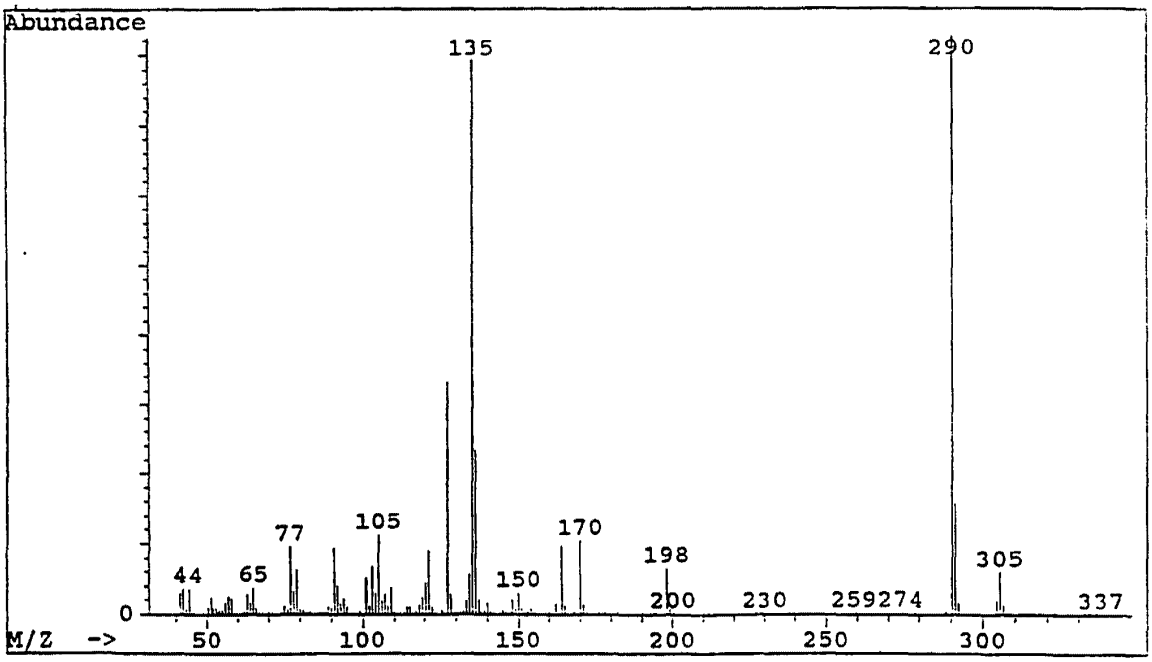
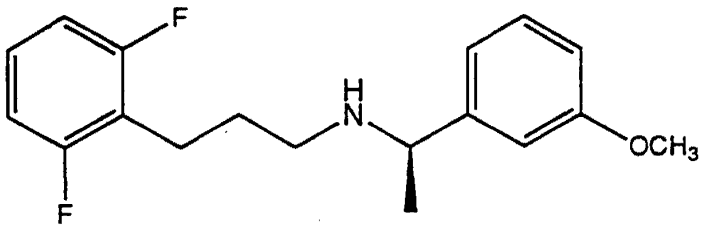


FIGURE 80

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



24L

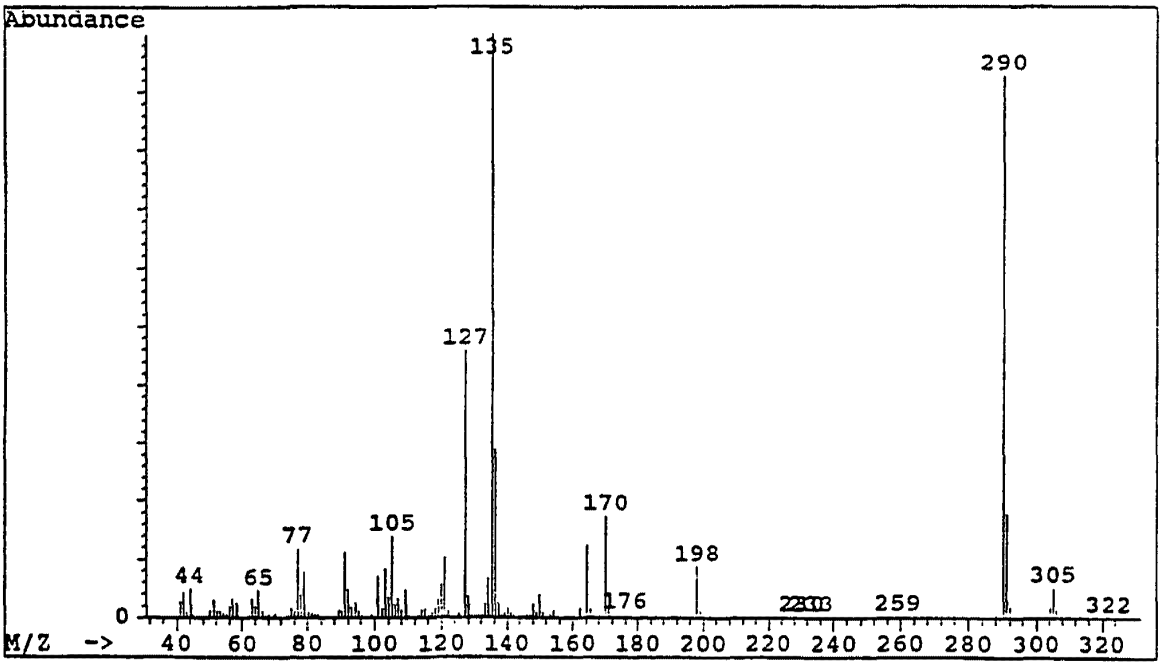
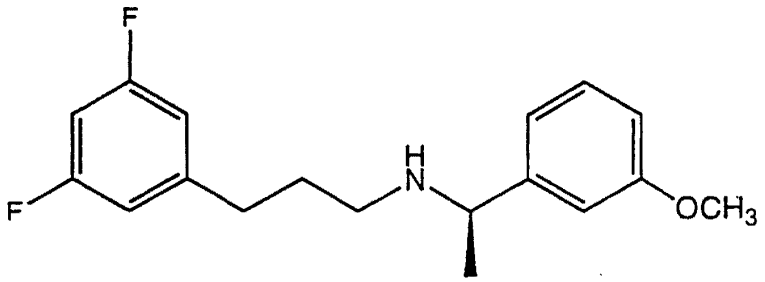


FIGURE 81

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



24M

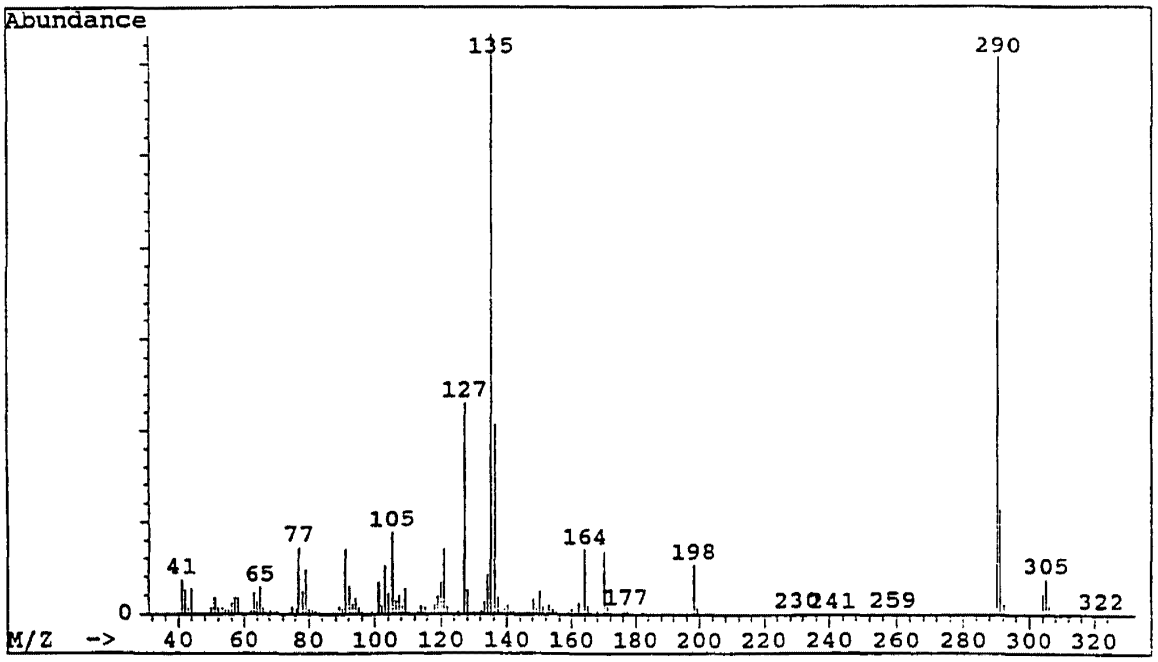
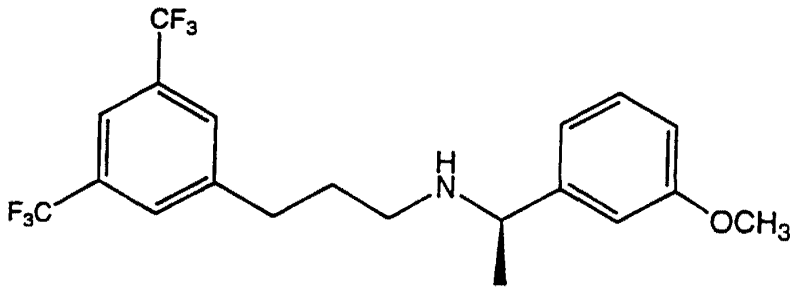


FIGURE 82

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)



24N

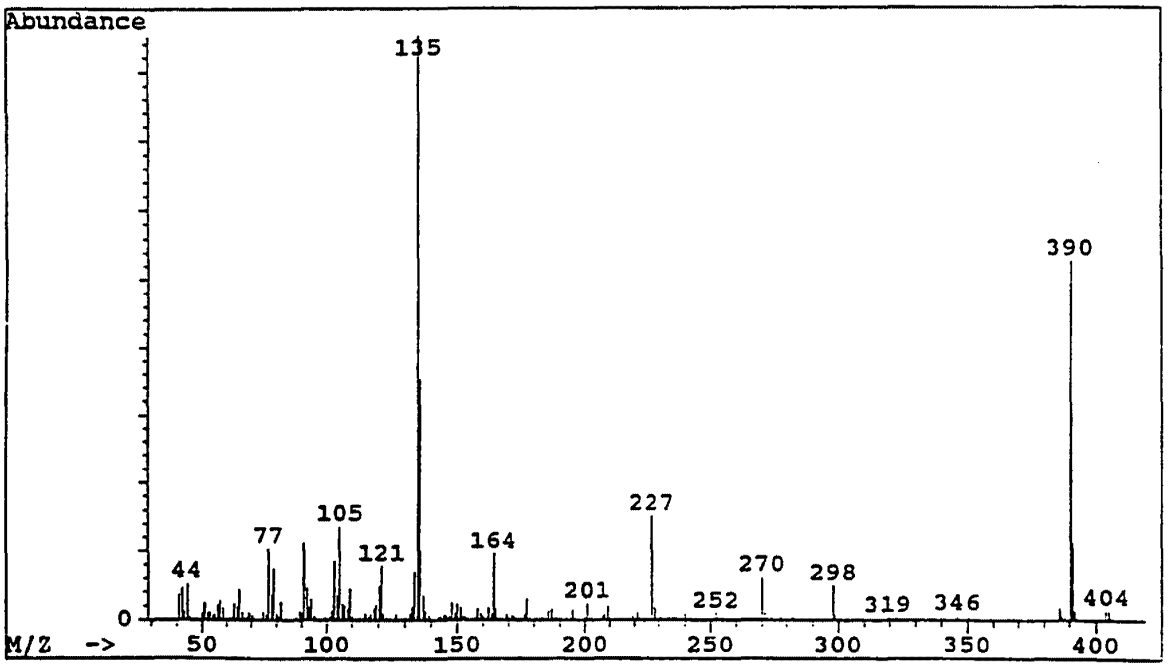


FIGURE 83

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

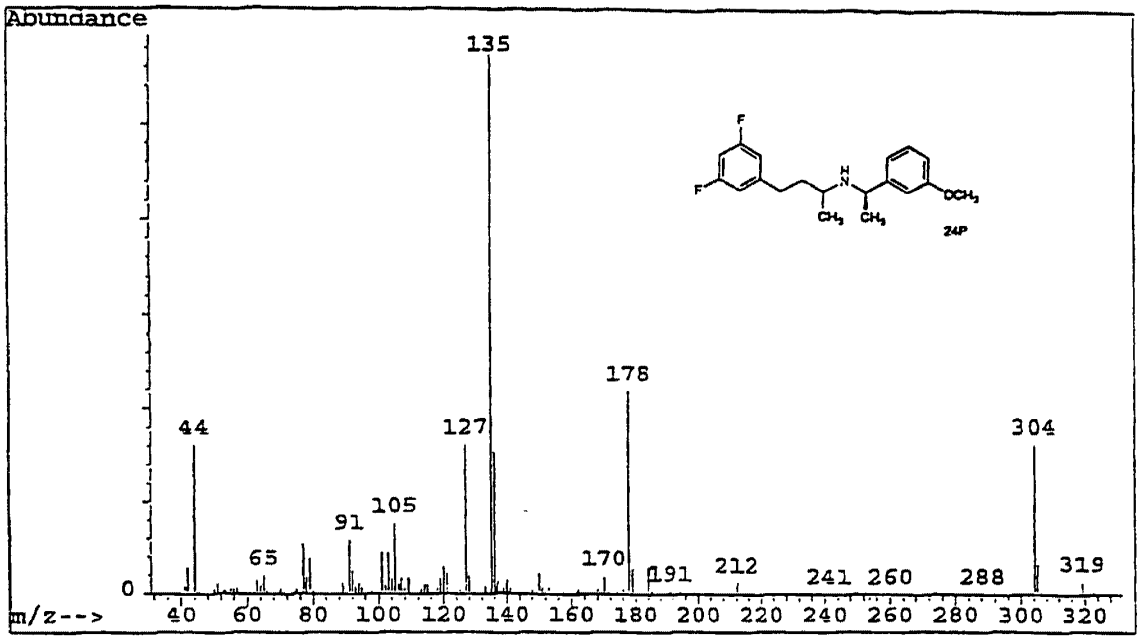


FIGURE 84

MASS SPECTRA OF NPS COMPOUNDS (ELECTRON IMPACT, 70eV)

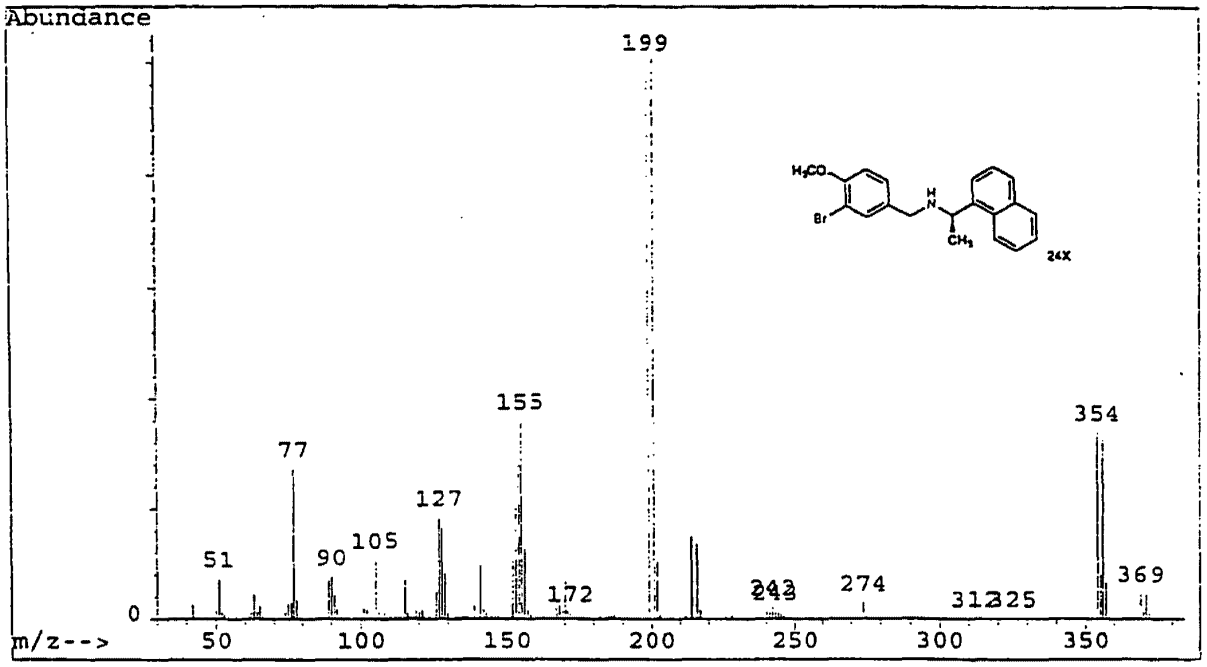


FIGURE 85

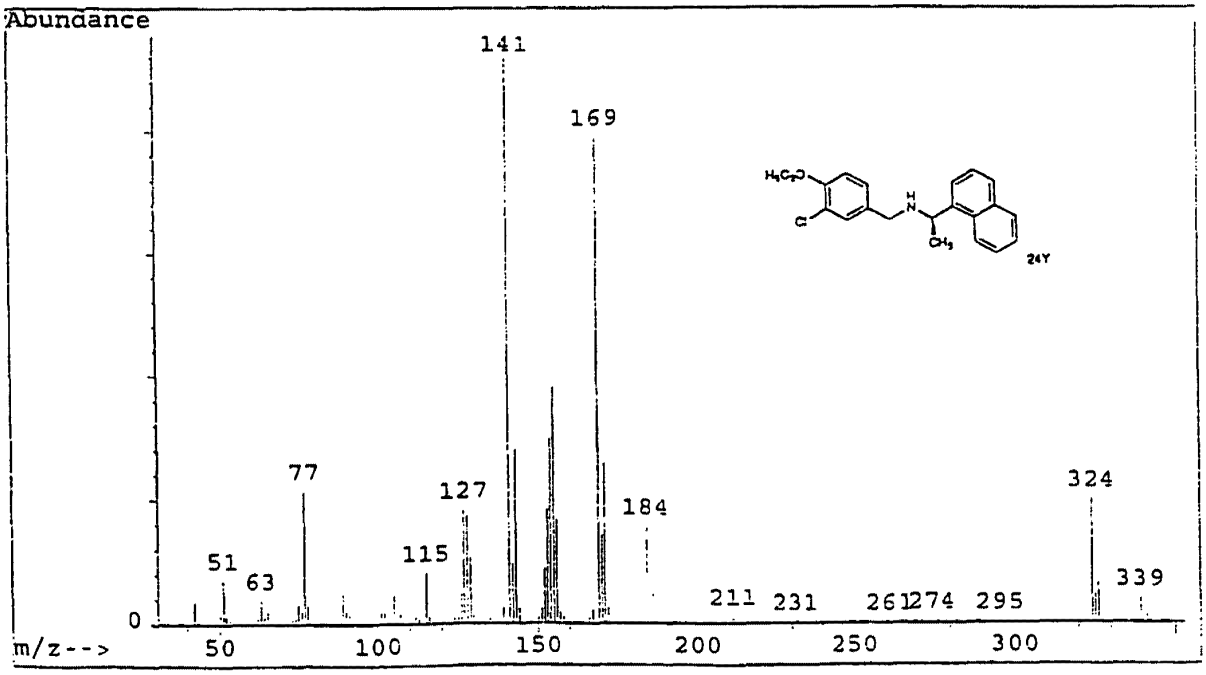


FIGURE 86

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

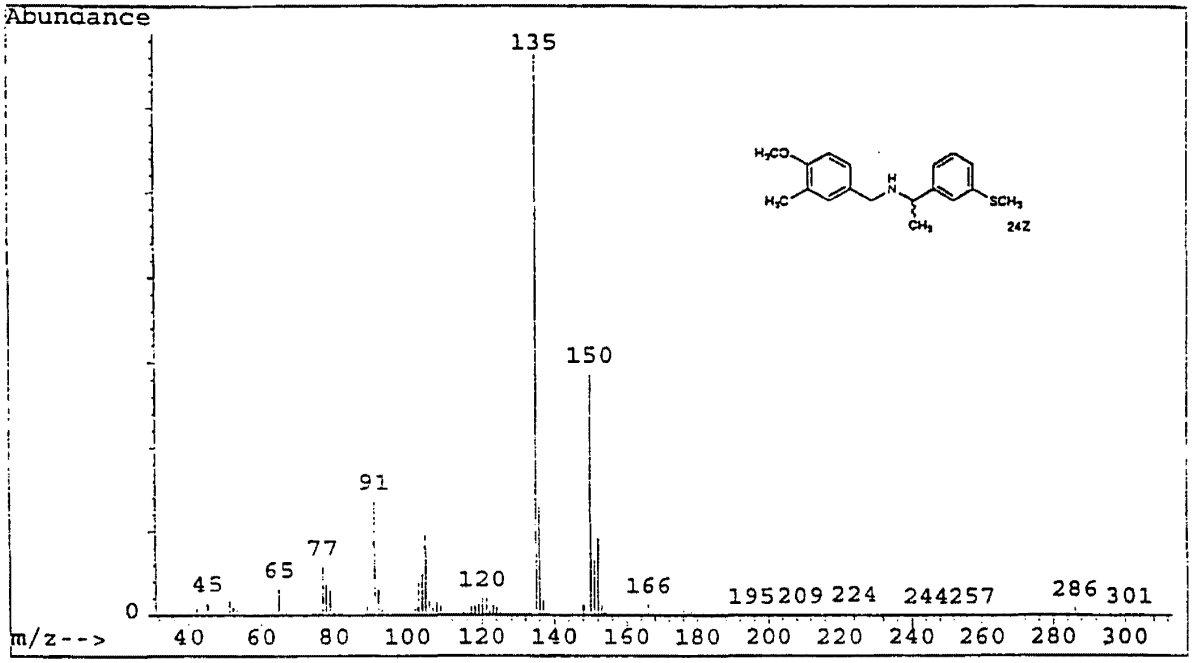


FIGURE 87

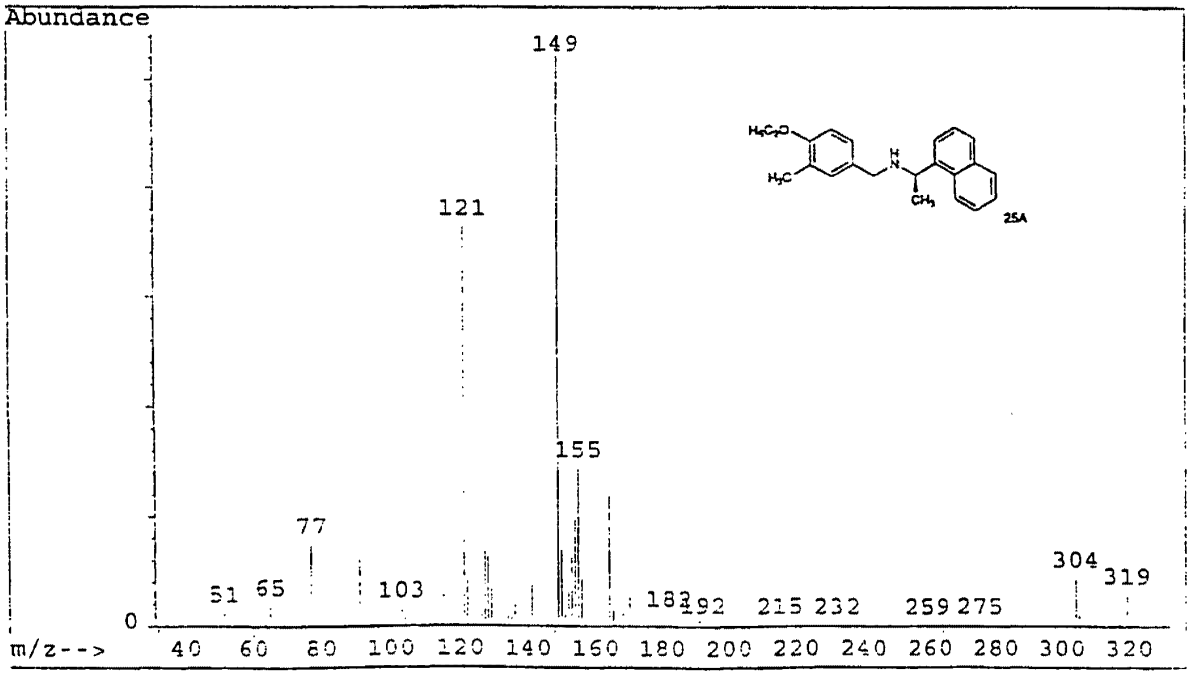


FIGURE 88

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

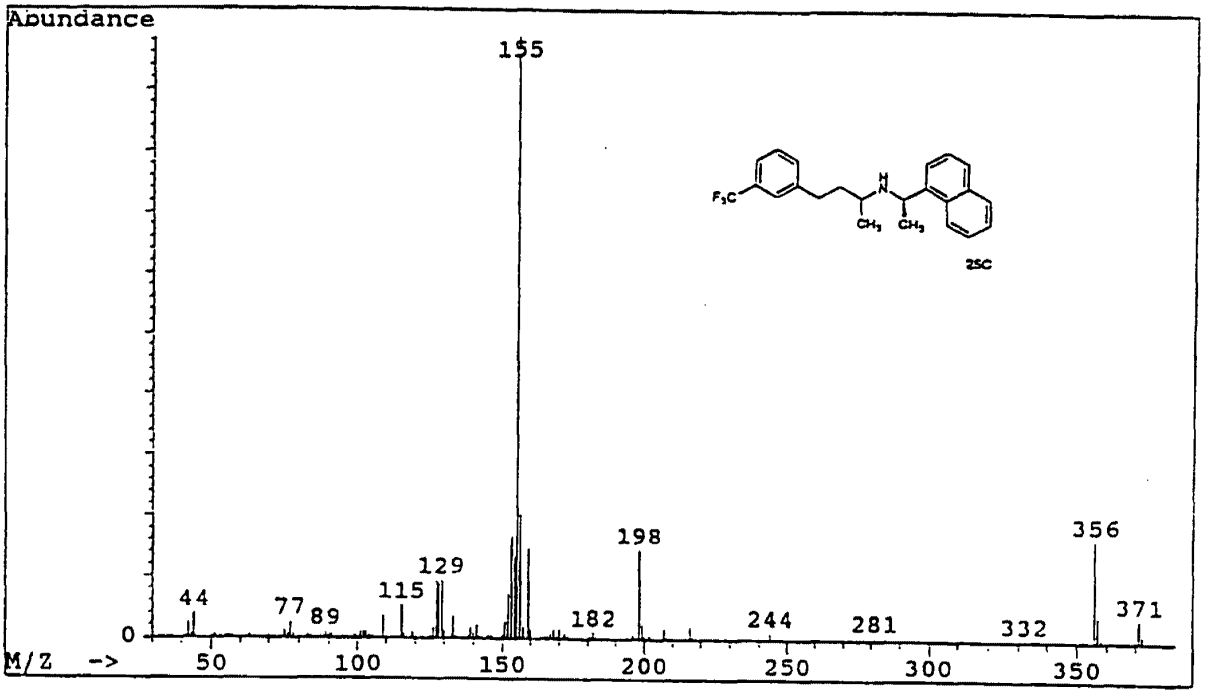


FIGURE 89

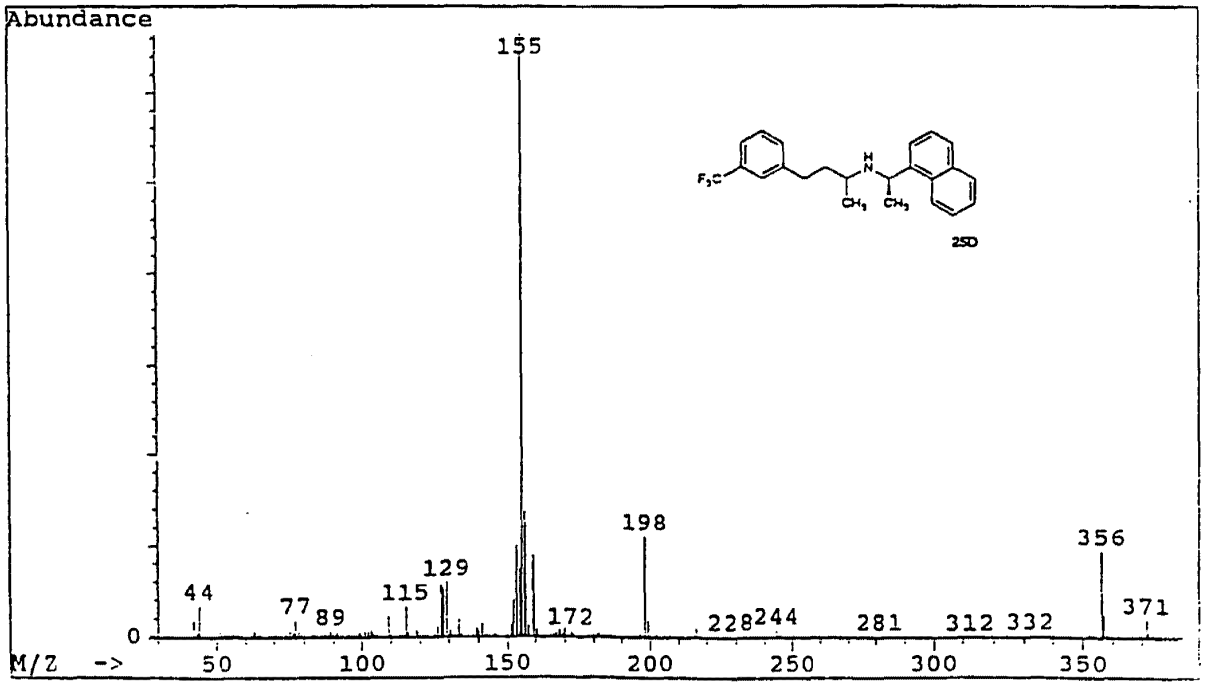


FIGURE 90

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

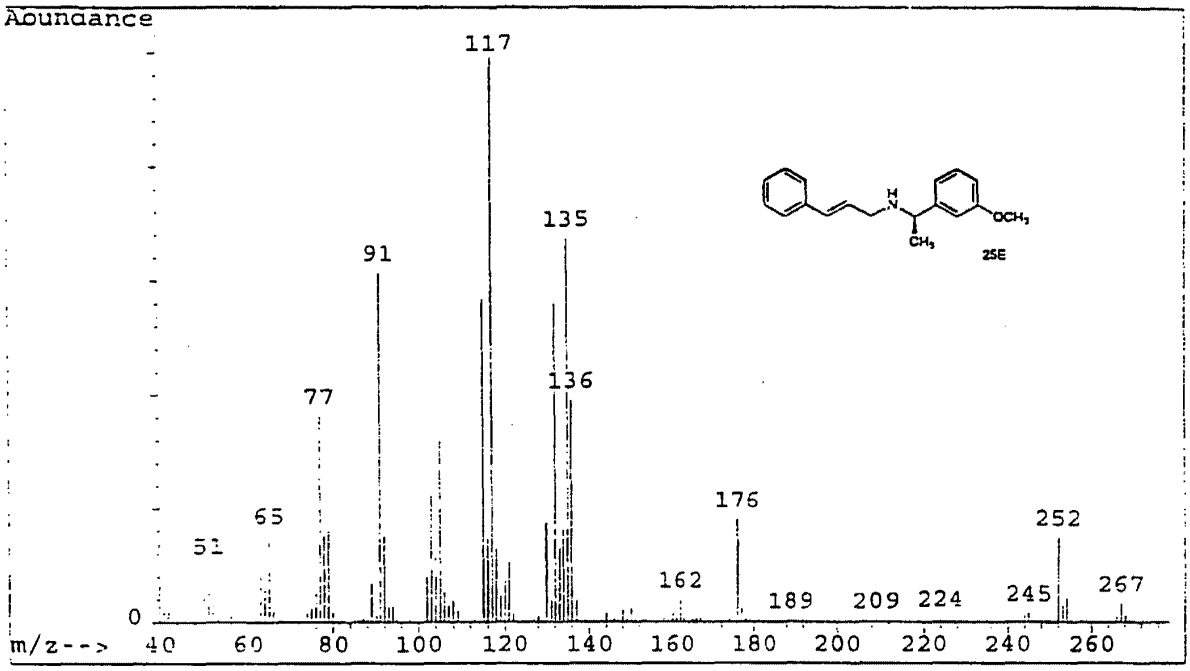


FIGURE 91

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

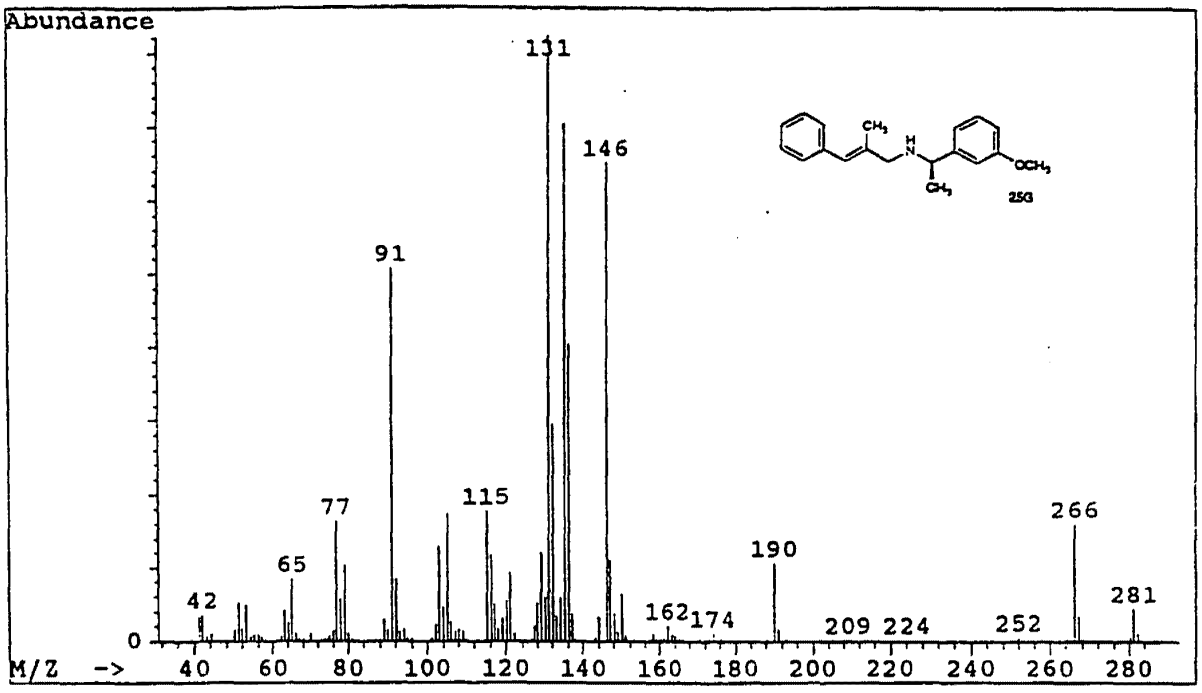


FIGURE 92

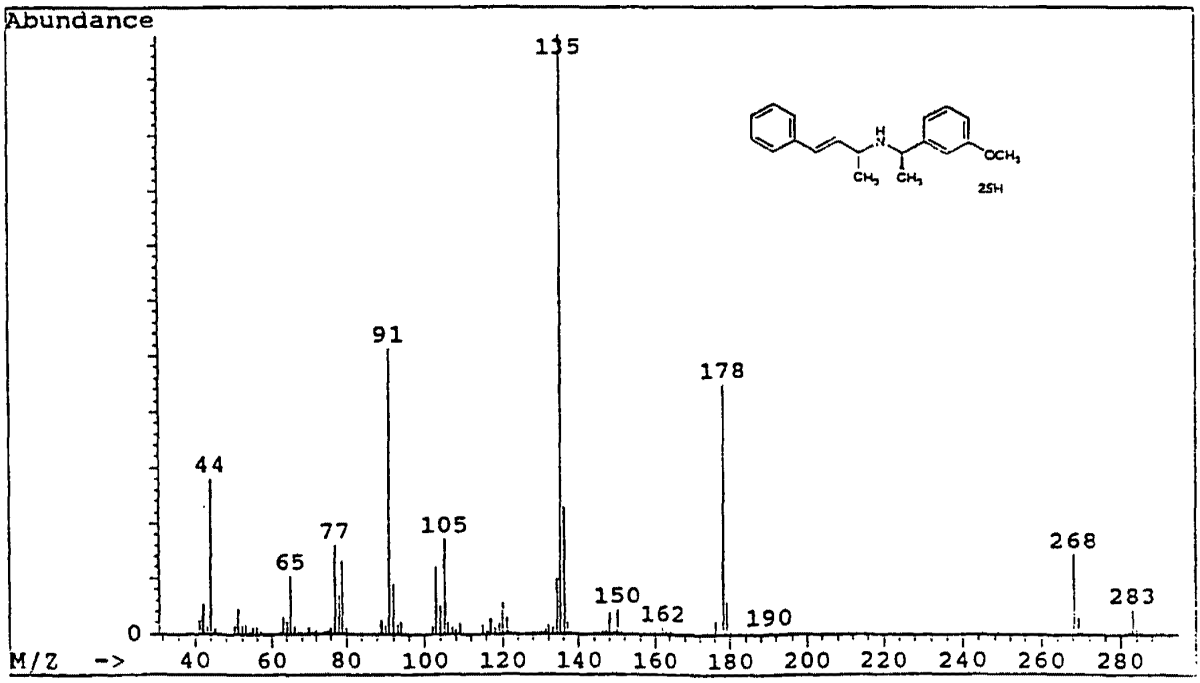


FIGURE 93

MASS SPECTRA OF NPS COMPOUNDS
(ELECTRON IMPACT, 70eV)

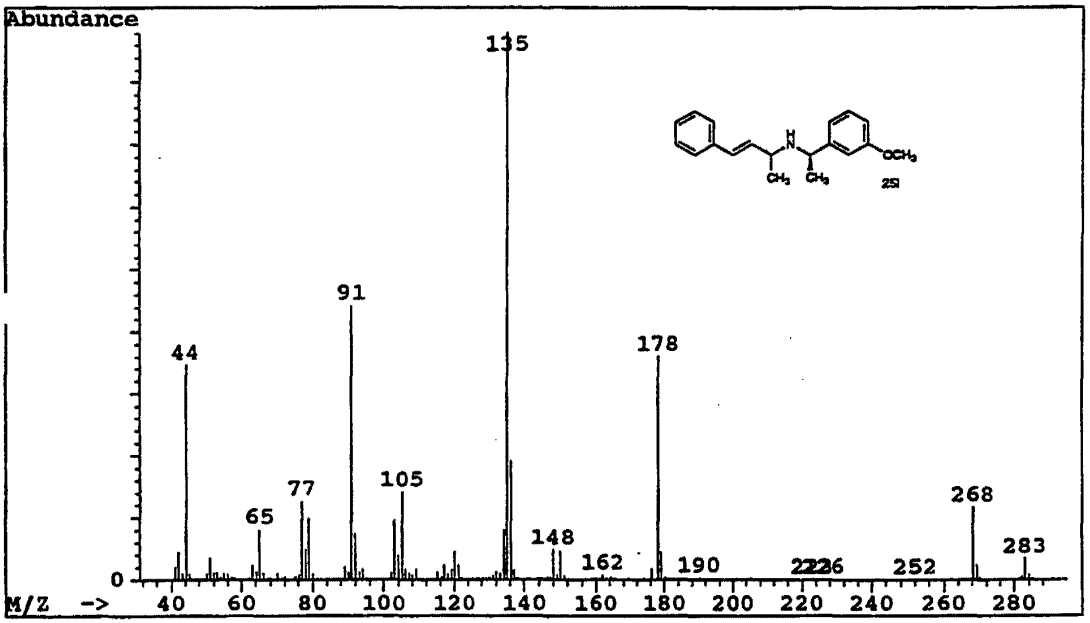


FIGURE 94

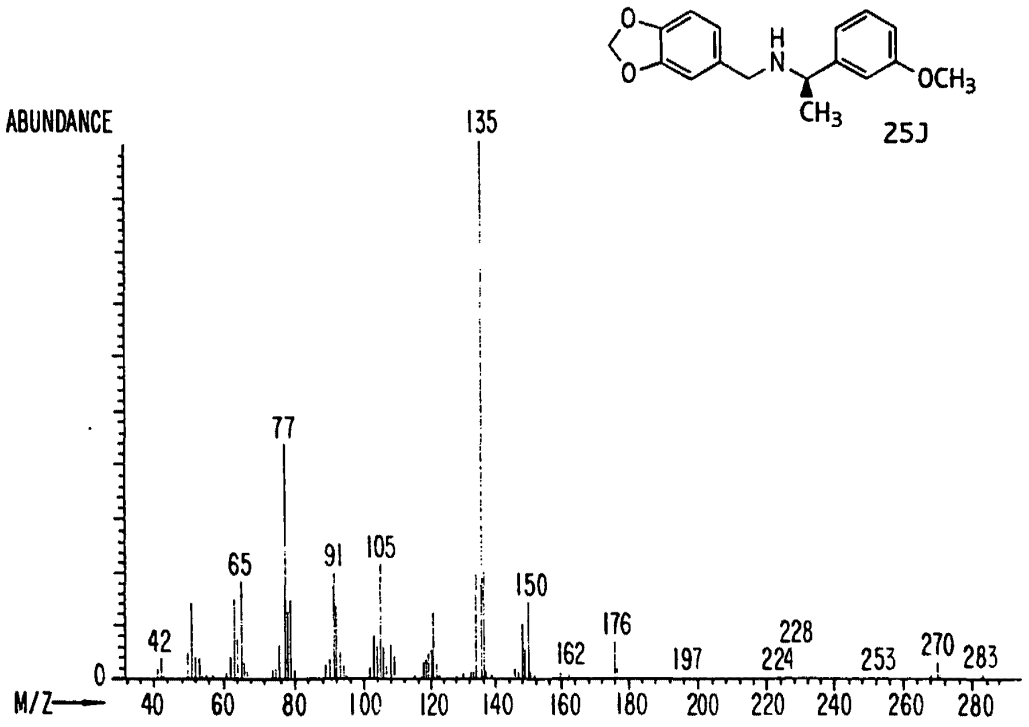
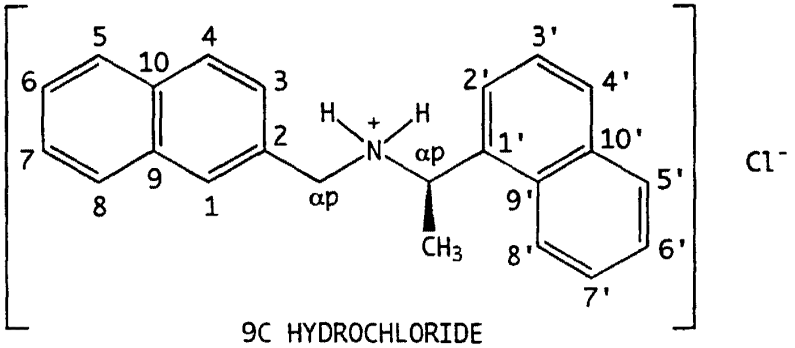

ABUNDANCE
135
77
65
91
105
150
42
176
162
197
228
224
253
270
283
0
M/Z
40
60
80
100
120
140
160
180
200
220
240
260
280
O
O
H
N
OCH3
CH3
25J

FIG. 95.

FIG. 96.

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

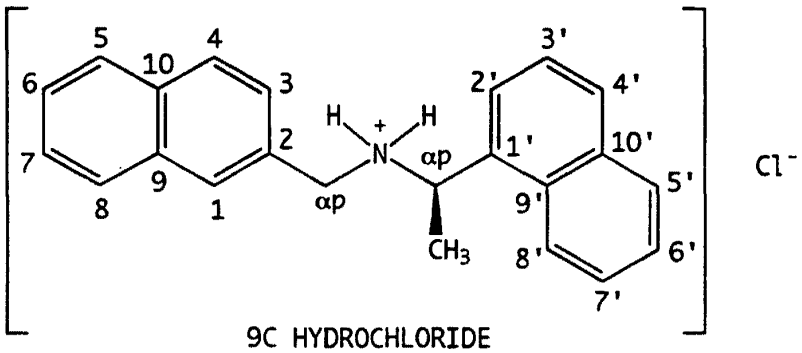


9C HYDROCHLORIDE

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:



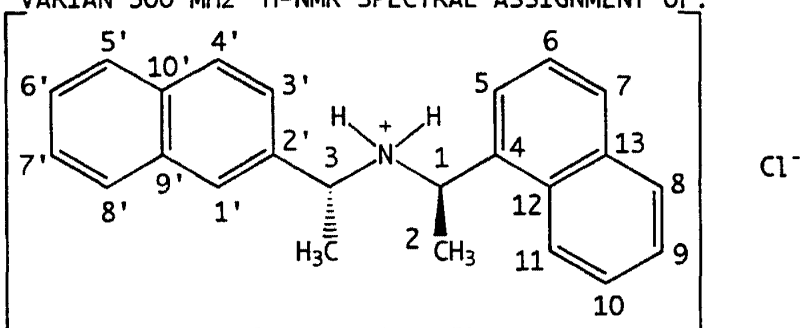
9C HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCI 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:



9R HYDROCHLORIDE

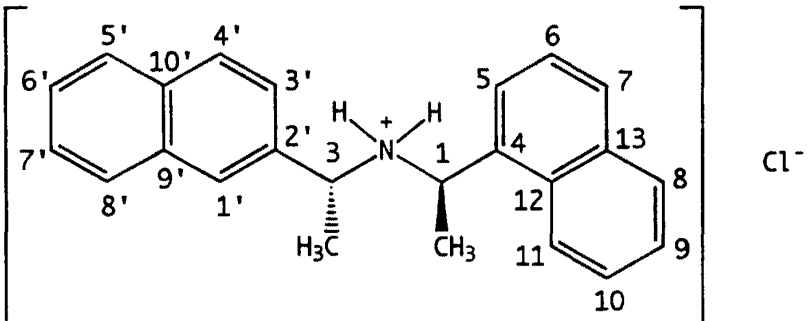
NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# OF H's	δ(PPM)	MULTIPLICITY	COUPLING (Hz)	ASSIGNMENT
3H	1.97	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:

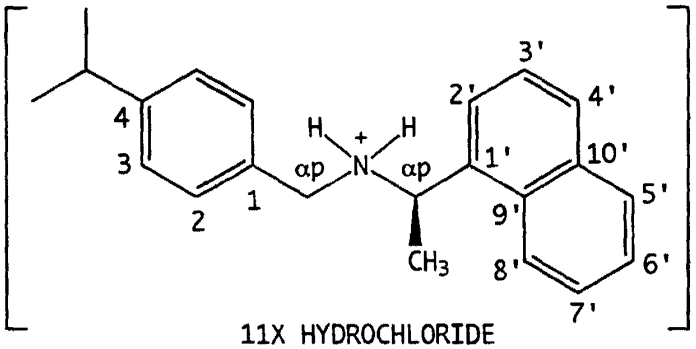


9R HYDROCHLORIDE

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:



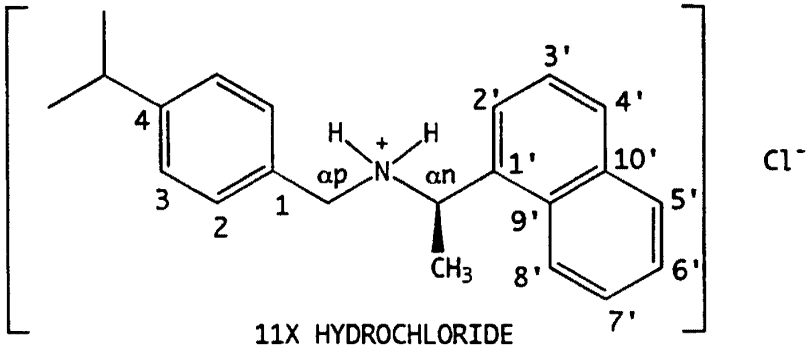
11X HYDROCHLORIDE

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
6H	1.17	d	J=7.1	$-CH(CH_3)_2$
3H	1.86	d	J=6.8	aliph-CH_3
1H	2.84	p	J=7.0	$-CH(CH_3)_2$
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:



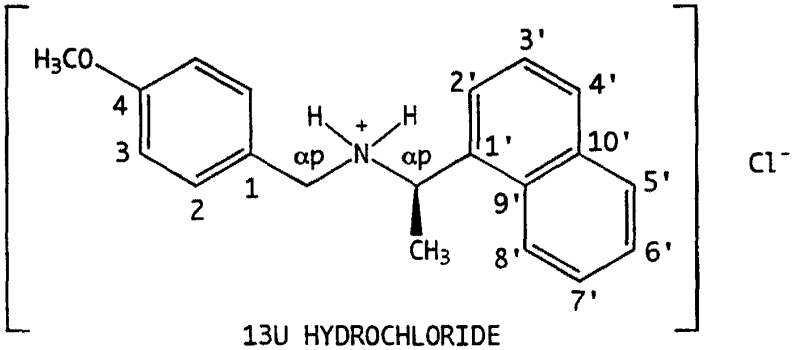
11X HYDROCHLORIDE

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	-$CH(CH_3)_2$
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

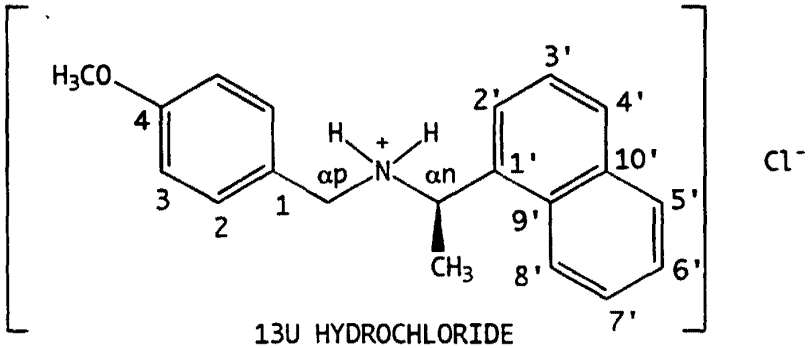
NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-5 PPM ARE IN 1% MeOD/$CDCl_3$ (5mg/mL). RESONANCES FROM 5-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# 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. 102.

FIG. 103.

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

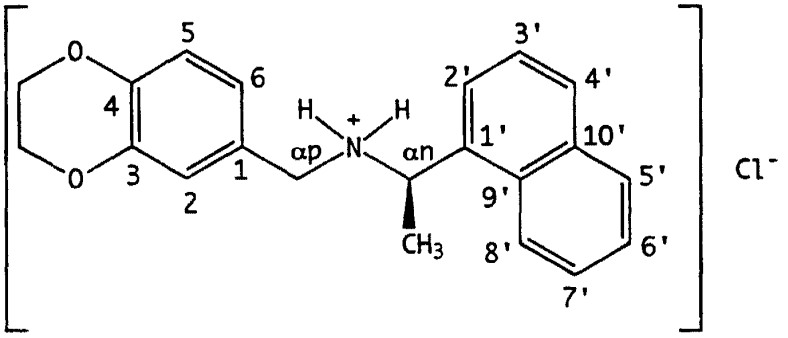


13U HYDROCHLORIDE

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:



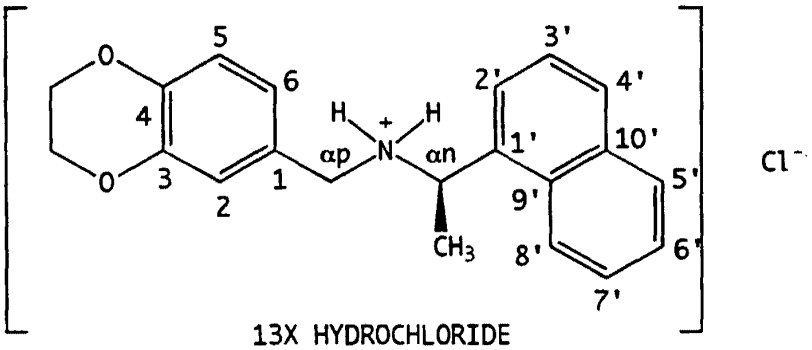
13X HYDROCHLORIDE

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

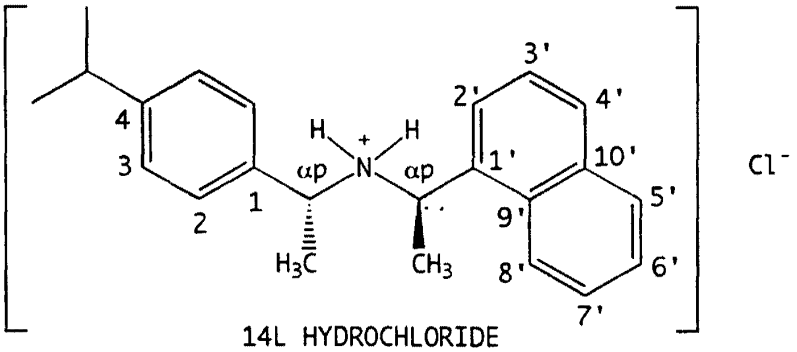
NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

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-CH_2-CH_2-O-
64.09	CH_2	-O-CH_2-CH_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-C-arom
144.17	Q	-O-C-arom

FIG. 105.

SUBSTITUTE SHEET (RULE 26)

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



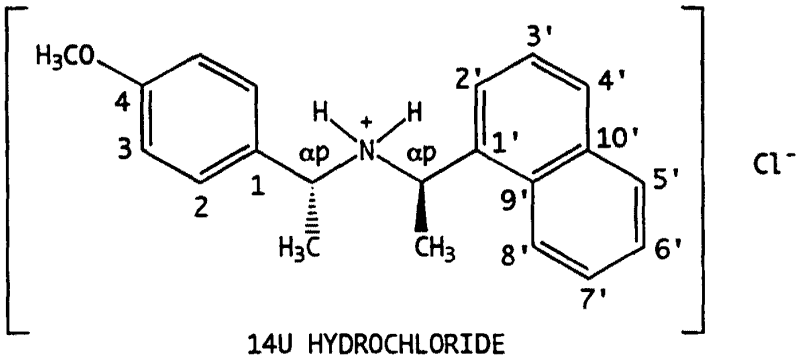
14L HYDROCHLORIDE

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	$-CH(CH_3)_2$
3H	1.242	d	J=6.9	$-CH(CH_3)_2$
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	$-CH(CH_3)_2$
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

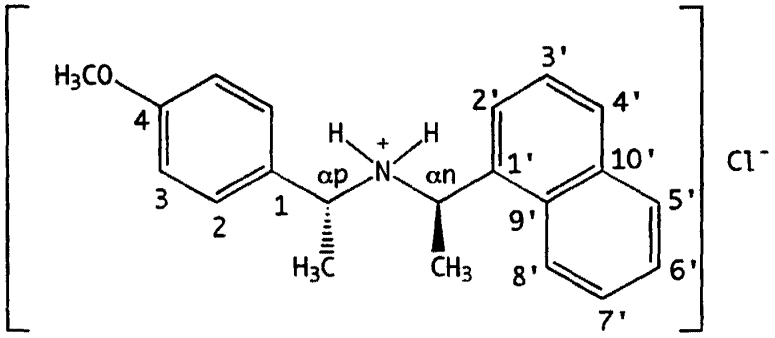
NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-10 PPM ARE IN 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 10-12 PPM ARE IN $CDCl_3$ (60 mg/mL).

# 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.

SUBSTITUTE SHEET (RULE 26)

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



14U HYDROCHLORIDE

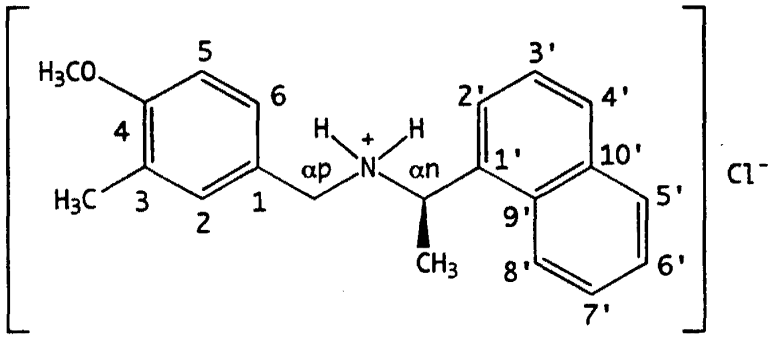
NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ (60 mg/mL).

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.

SUBSTITUTE SHEET (RULE 26)

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



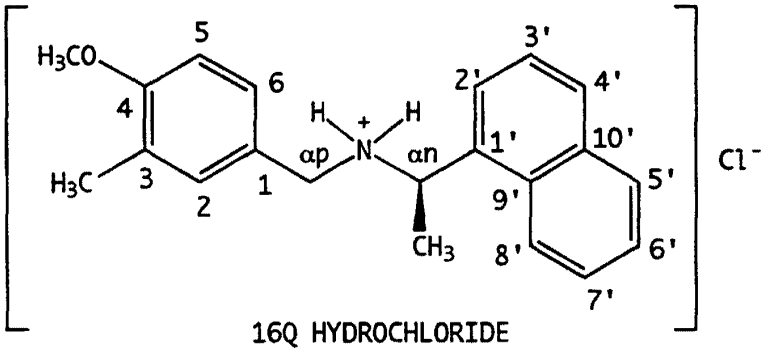
16Q HYDROCHLORIDE

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:



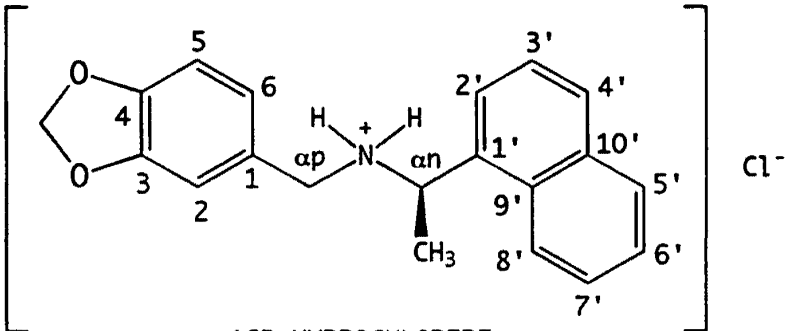
16Q HYDROCHLORIDE

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:



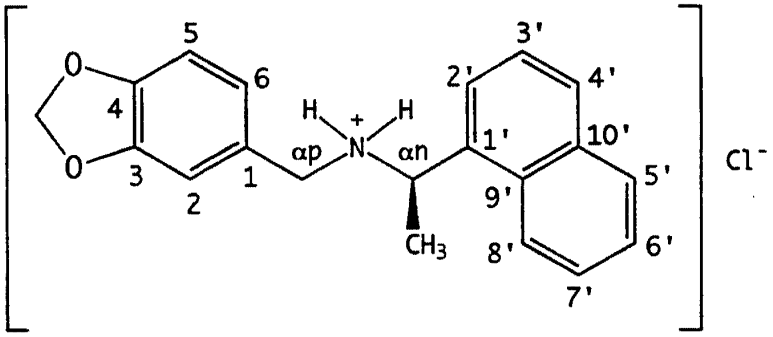
16R HYDROCHLORIDE

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:



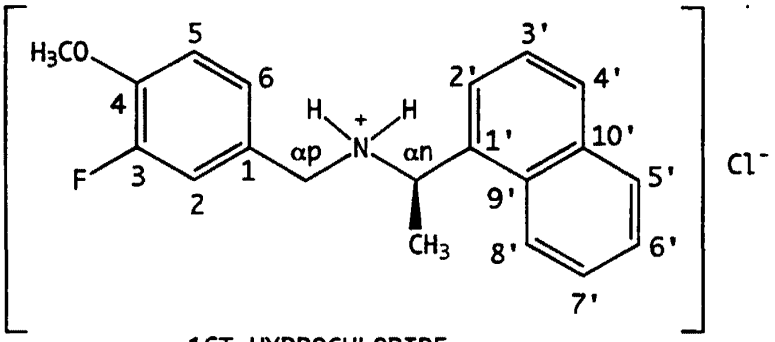
16R HYDROCHLORIDE

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-CH_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-C-arom
148.26	Q	-O-C-arom

FIG. 112.

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



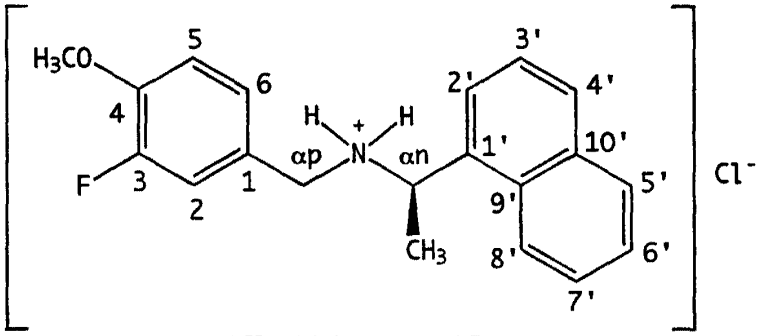
16T HYDROCHLORIDE

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:



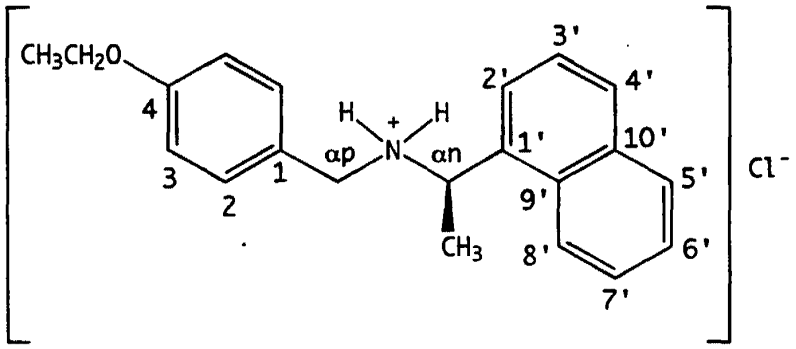
16T HYDROCHLORIDE

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:



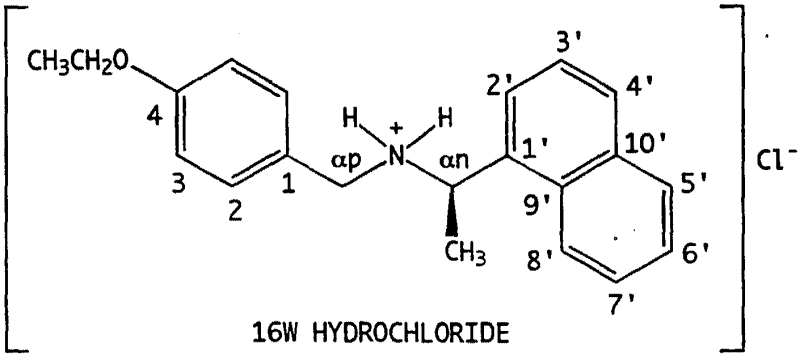
16W HYDROCHLORIDE

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:



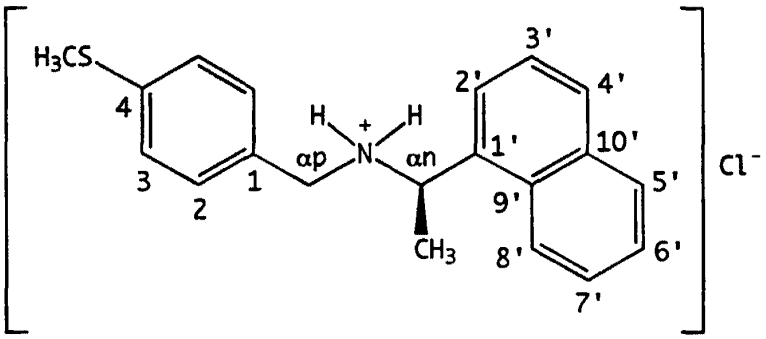
16W HYDROCHLORIDE

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:



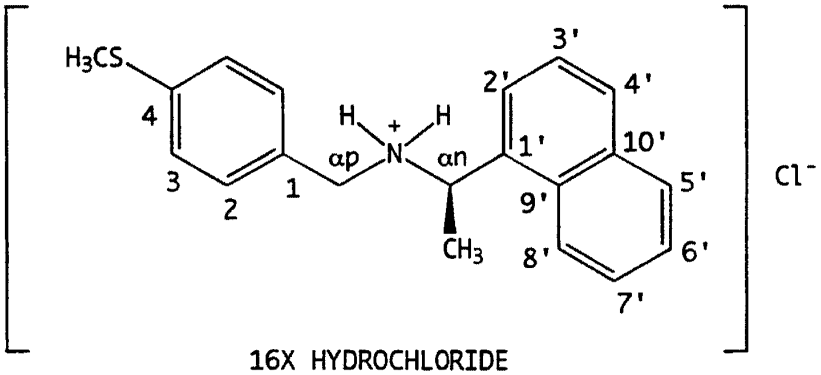
16X HYDROCHLORIDE

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:



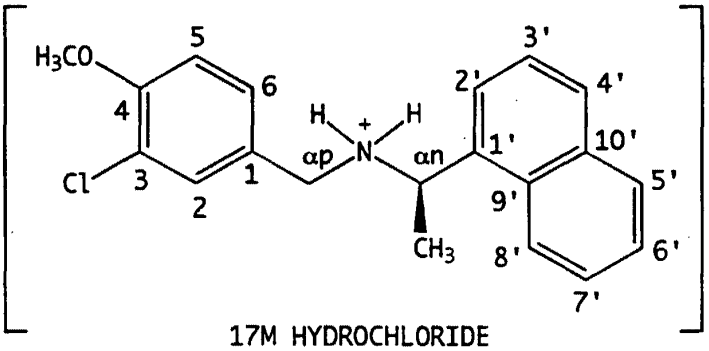
16X HYDROCHLORIDE

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:



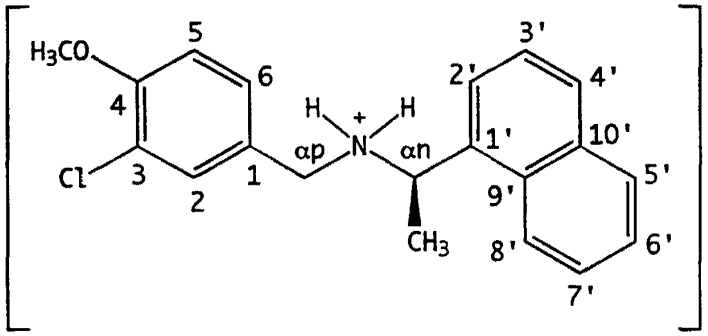
17M HYDROCHLORIDE

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	1.88	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.

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



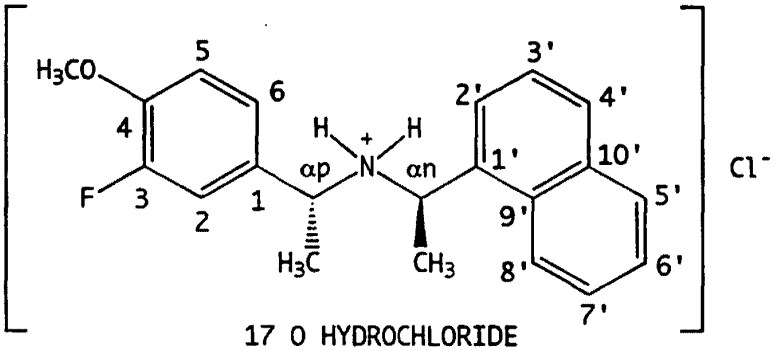
17M HYDROCHLORIDE

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

δ(PPM)	MULTIPLICITY	ASSIGNMENT
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	RIGHT SIDE
122.27	Q	LEFT SIDE arom-C-CH_2NH_2
122.65	Q	arom-C-Cl
125.14	CH	RIGHT SIDE
126.01	CH	RIGHT SIDE
126.14	CH	RIGHT SIDE
127.05	CH	RIGHT SIDE
129.21	CH	RIGHT SIDE
129.35	CH	
130.30	Q	RIGHT SIDE
130.69	CH	RIGHT SIDE
132.09	Q	RIGHT SIDE
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:



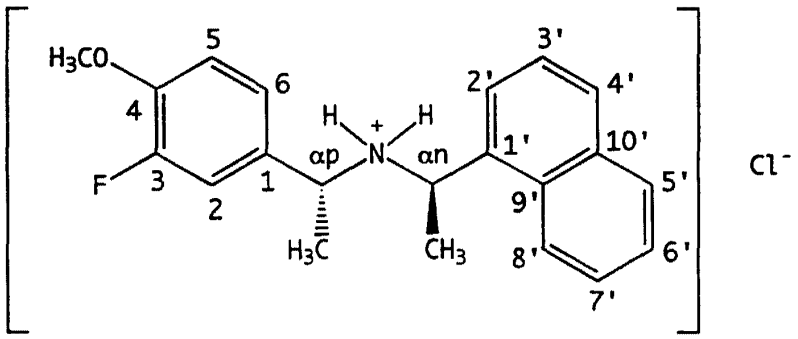
17 O HYDROCHLORIDE

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.

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



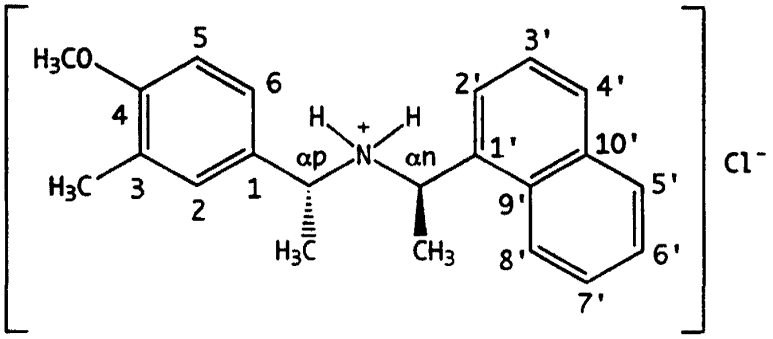
17 O HYDROCHLORIDE

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

20.89	CH_3	aliph-CH_3
21.78	CH_3	arom-CH_3
51.26	CH	-CH-
56.12	CH_3	O-CH_3
56.19	CH	-CH-
113.44	CH	
116.27	CH	
116.52	CH	
121.31	CH	
124.39	CH	
124.43	CH	
125.24	CH	
125.97	CH	
126.03	CH	
126.45	CH	
128.35	Q	
128.43	Q	
128.98	CH	
129.10	CH	
130.05	Q	
132.45	Q	
133.61	Q	
147.96	Q	
148.10	Q	
150.26	Q	
153.55	Q	

FIG. 122.

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



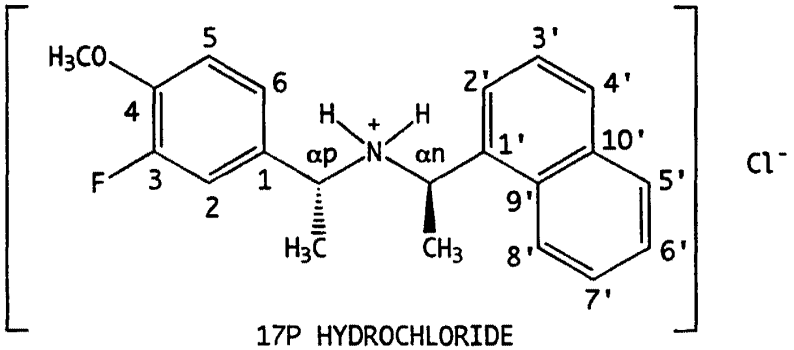
17P HYDROCHLORIDE

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	1.82	d	J=6.7	phenyl-CH_3
3H	1.83	d	J=6.7	naphthyl-CH_3
3H	1.93	s	n.a.	arom-CH_3
3H	3.83	s	n.a.	-OCH_3
1H	3.90	q	J=6.9	phenyl-CH-
1H	4.74	q	J=7.0	naphthyl-CH-
1H	6.52	d	J=1.6	2
1H	6.70	d	J=8.5	5
1H	7.03	dd	J_1=8.4, J_2=2.2	6
1H	7.17	bd	J=9.2	8'
1H	7.34	dd	$J_1=J_2$=8.4	7'
1H	7.51	dd	$J_1=J_2$=8.2	6'
1H	7.68	dd	$J_1=J_2$=7.9	3'
1H	7.91	d	J=8.0	4' OR 5'
1H	7.92	d	J=7.8	4' OR 5'
1H	8.21	bd	J=6.6	2'
1H	8.65	bs	n.a.	aliph-NH_2+
1H	10.58	bs	n.a.	aliph-NH_2+

FIG. 123.

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



17P HYDROCHLORIDE

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

δ(PPM)	MULTIPLICITY	ASSIGNMENT
15.7	CH_3	arom-CH_3
20.5	CH_3	phenyl-CH_3
21.6	CH_3	naphthyl-CH_3
51.0	CH	naphthyl-CH-
55.2	CH_3	O-CH_3
56.3	CH	phenyl-CH-
110.2	CH	5
121.5	CH	8' OR 6'
124.8	CH	2'
125.8	CH	3' OR 6'
125.8	CH	3' OR 6'
126.3	CH	7'
126.5	CH	8' OR 6'
126.6	Q	
127.0	Q	
128.8	CH	4' OR 5'
129.0	CH	4' OR 5'
130.1	Q	
130.9	CH	2
132.6	Q	
133.6	Q	
158.1	Q	

FIG. 124.

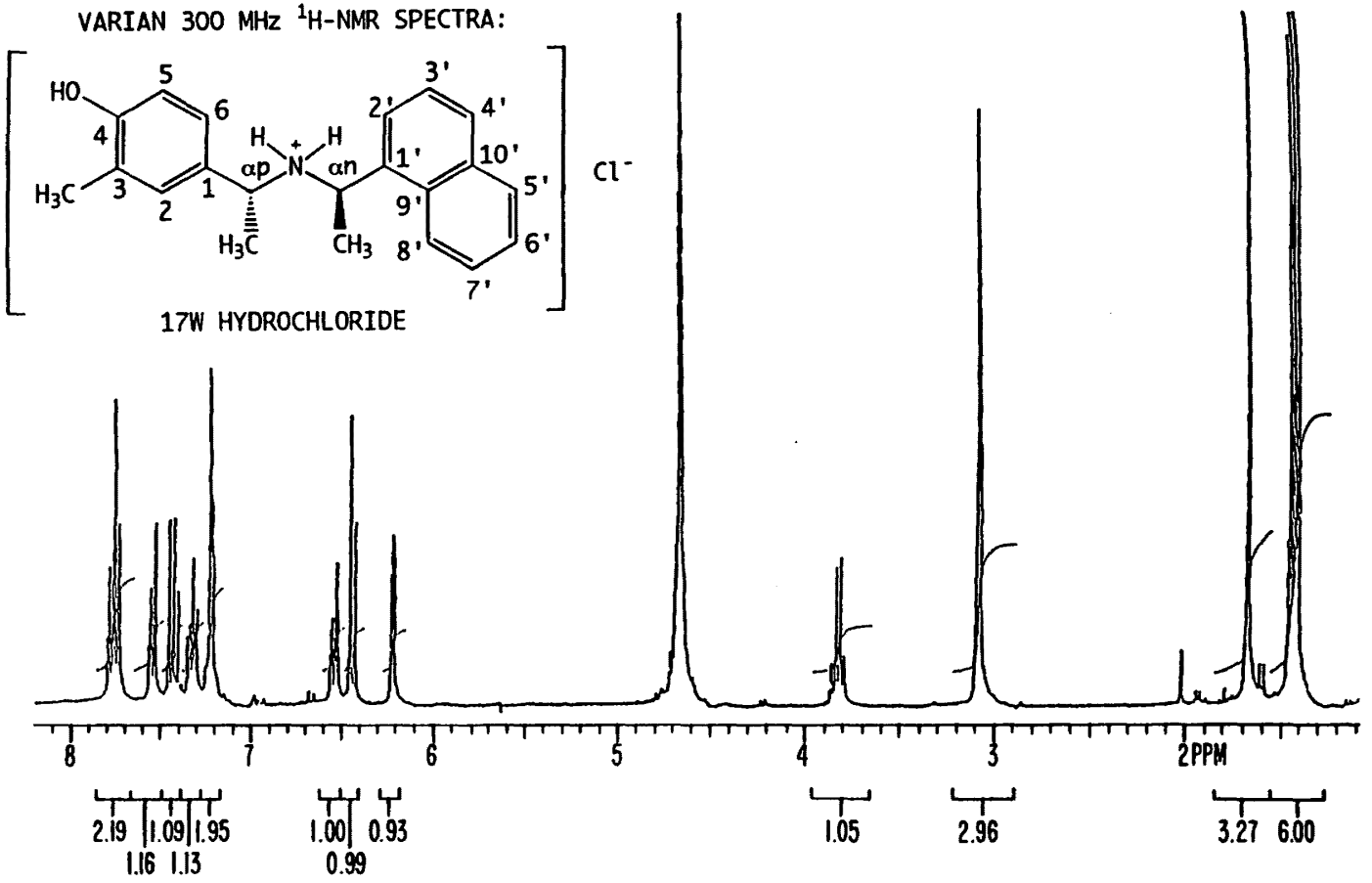
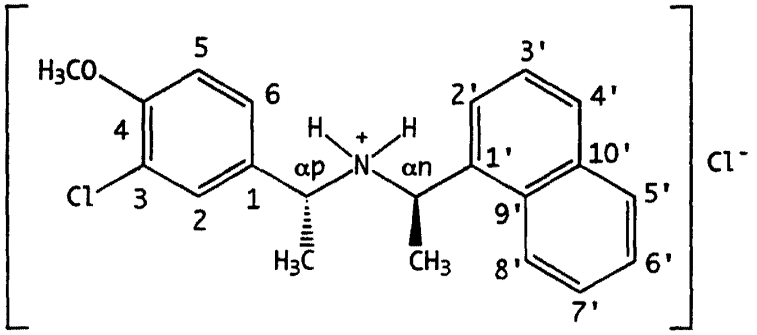


FIG. 125. NMR SPECTRA ARE OF THE HCl SALT. RESONANCES FROM 0-10 PPM ARE 1% MeOD/$CDCl_3$ (5 mg/mL). RESONANCES FROM 10-12 PPM IN $CDCl_3$ (60 mg/mL)

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



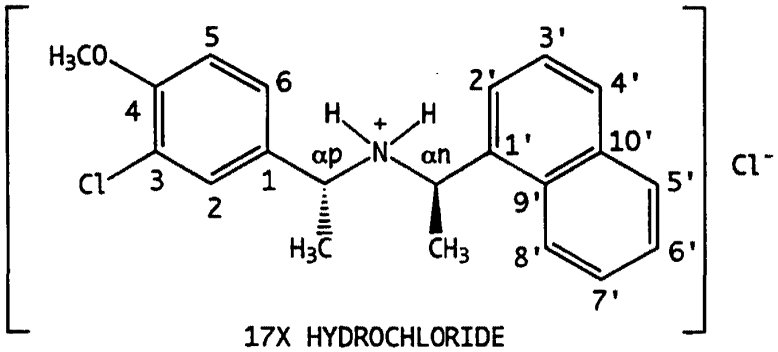
17X HYDROCHLORIDE

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	1.86	d	J=7.0	phenyl-CHC$\underline{H}_3$
3H	1.90	d	J=6.8	naphthyl-CHC$\underline{H}_3$
3H	3.90	s	n.a.	-OCH_3
1H	3.91	q	J=~6.4	phenyl-C$\underline{H}$CH_3
1H	4.79	q	J=6.7	naphthyl-C$\underline{H}$CH_3
1H	6.79	d	J=2.0	2
1H	6.84	d	J=8.5	5
1H	7.19	bd	J=7.6	8'
1H	7.26	dd	J_1=8.4,J_2=1.7	6
1H	7.38	dd	J_1=J_2=7.0	7'
1H	7.52	dd	J_1=J_2=8.1	6'
1H	7.69	dd	J_1=J_2=8.1	3'
1H	7.92	d	J=8.2	4' OR 5'
1H	7.94	d	J=8.1	4' OR 5'
1H	8.30	bd	J=5.0	2'
2H	10.72	vbs	n.a.	aliph-NH_2+

FIG. 126.

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



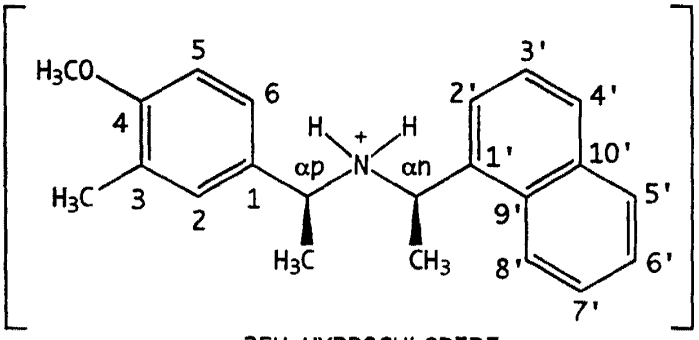
17X HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ + 1% MeOD (20 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
---	---	
20.6	CH_3	phenyl-CH<u>C</u>H_3
21.7	CH_3	naphthyl-CH<u>C</u>H_3
51.2	CH	naphthyl-<u>C</u>HCH$_3$
55.9	CH	phenyl-<u>C</u>HCH$_3$
56.2	CH_3	O-CH_3
112.4	CH	5
121.2	CH	8'
122.5	Q	
125.1	CH	2'
125.9	CH	3'
126.2	CH	6'
126.8	CH	6 OR 7'
127.6	CH	6 OR 7'
128.4	Q	
129.0	CH	4' OR 5'
129.3	CH	4' OR 5'
130.1	Q	
130.7	CH	2'
132.2	Q	
133.7	Q	
155.4	Q	3

FIG. 127.

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



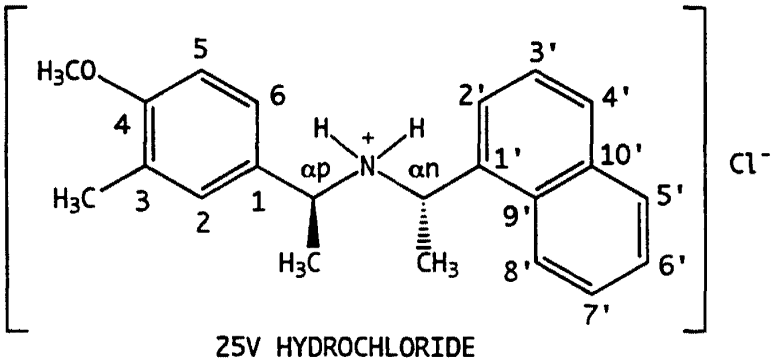
25U HYDROCHLORIDE

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	1.74	d	J=6.7	aliph-CH3
3H	1.90	d	J=6.0	aliph-CH3
3H	2.23	s	n.a.	arom-CH3
3H	3.88	s	n.a.	-OCH3
1H	4.25	bd	J=7.3	-CH-
1H	4.90	bq	J=6.5	-CH-
1H	6.87	d	J=8.4	
1H	7.17	bs	n.a.	
1H?	7.20-7.27	m	n.a.	
2H?	7.35-7.46	m	n.a.	
1H	7.50	dd	J1=J2=8.1	
1H	7.59	dd	J1=J2=7.9	
1H	7.87	d	J=6.7	
1H	7.89	d	J=6.6	
1H	8.02	d	J=7.0	
1H	8.97	bs	n.a.	$-NH_2+-$
1H	10.83	bs	n.a.	$-NH_2+-$

FIG. 128.

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



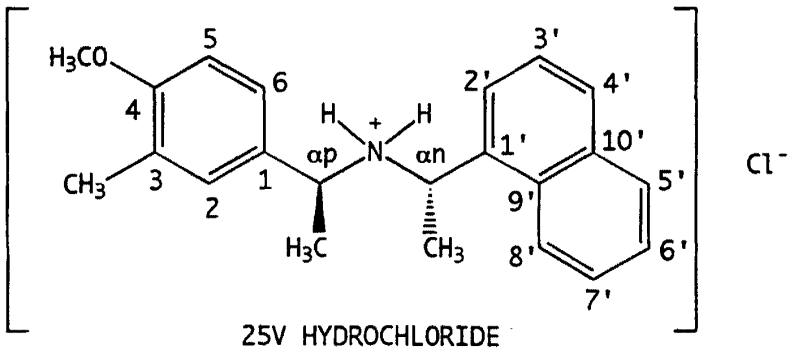
25V HYDROCHLORIDE

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
9H	1.92	bs	n.a.	phenyl-CH_3 naphthyl-CH_3 arom-CH_3
3H	3.83	s	n.a.	-OCH_3
1H	3.95	bq	J=6.0	phenyl-CH-
1H	4.79	bq	J=5.5	naphthyl-CH-
1H	6.57	bs	n.a.	2
1H	6.71	d	J=8.2	5
2H	7.10-7.17	m	n.a.	
1H	7.30-7.35	m	n.a.	
1H	7.50	dd	$J_1=J_2=7.7$	6'
1H	7.70	dd	$J_1=J_2=7.3$	3'
1H	7.91	d	J=7.8	4' OR 5'
1H	7.92	d	J=8.0	4' OR 5'
1H	8.39	bd	J=2.8?	2'
1H	8.63	bs	n.a.	aliph-NH_2+
1H	10.59	bs	n.a.	aliph-NH_2+

FIG. 129.

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



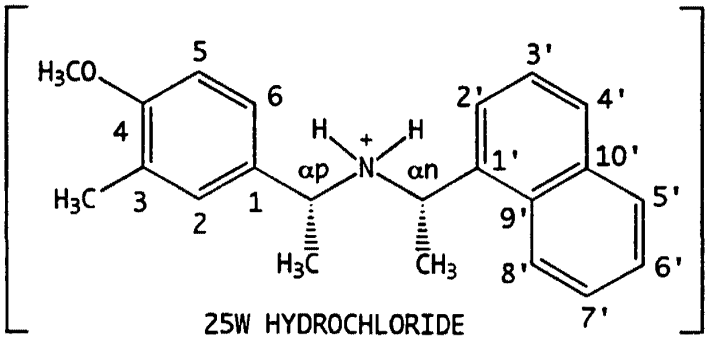
25V HYDROCHLORIDE

NMR SPECTRA ARE OF THE HCl SALT IN $CDCl_3$ + 1% MeOD (20 mg/mL).

δ(PPM)	MULTIPLICITY	ASSIGNMENT
15.8	CH_3	arom-CH3
20.97	CH_3	aliph-CH3
22.0	CH_3	aliph-CH3
51.2	CH	-CH-
55.4	CH_3	-OCH3
56.6	CH	-CH-
110.3	?	
121.8	CH	
125.5	CH	
125.8	CH	
125.2	CH	
126.3	CH	
126.9	CH	
127.0	Q	
127.2	CH	
128.8	Q	
128.9	?	
130.3	Q	
131.2	CH	
133.0	Q	
133.7	Q	
158.1	Q	

FIG. 130.

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



25W 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	1.74	d	J=6.1	aliph-CH3
3H	1.89	d	J=6.0	aliph-CH3
3H	2.24	s	n.a.	arom-CH3
3H	3.89	s	n.a.	-OCH3
1H	4.27	bq	J=6.2	-CH-
1H	4.92	bq	J=5.1	-CH-
1H	6.89	d	J=7.7	
1H	7.18	bs	n.a.	
1H	7.26	bd	J=7.9	
2H?	7.36-7.47	m	n.a.	
1H	7.51	dd	J1=J2=7.6	
1H	7.61	dd	J1=J2=7.5	
1H	7.88	d	J=8.0	
1H	7.90	d	J=7.5	
1H	7.99	d	J=6.9	
1H	9.10	bs	n.a.	$-NH_2+-$
1H	10.67	bs	n.a.	$-NH_2+-$

FIG. 131.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/13704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C211/27 C07C211/30 C07C217/58 C07C211/28 A61K31/135

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 18959 (BRIGHAM AND WOMEN'S HOSPITAL, INC., USA;NPS PHARMACEUTICALS, INC.) 1 September 1994 see claims 99-101 28-35; figure 36 ---	1-4, 8-10, 17-21
X	WO,A,93 04373 (NPS PHARMACEUTICALS, INC., USA) 4 March 1993 see page 28, line 22 - line 25; figure 36 --- -/--	1-4, 8-10, 17-21

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

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
12 April 1996	17.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Seufert, G

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 121, no. 19, 7 November 1994 Columbus, Ohio, US; abstract no. 230462, KOMEYOSHI, YUKIO ET AL 'Optically active amines and their manufacture, intermediates, and uses' see RN 158075-03-7, 158075-02-6, 158075-01-5, 158075-00-4, 158074-98-7, 158074-97-6 see abstract & JP,A,06 116 214 (SUMITOMO CHEMICAL CO, JAPAN) ---	1,17
X	EP,A,0 508 307 (SUMITOMO CHEMICAL CO., LTD., JAPAN) 14 October 1992 see claim 1; examples 12-14,17-23 ---	1,2,5,6, 17
X	DE,A,25 41 184 (CHINOIN GYOGYSZER ES VEGYESZET) 15 April 1976 see page 3, compound II, page 8, line 4 ---	16
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 25, no. 6, 1982 WASHINGTON US, pages 670-679, J. E. CLIFTON ET AL. 'Arylethanolamines derived from Salicylamide with .alpha. and .beta.-adrenoceptor blocking activity.' see page 673, compound 84 ---	1
X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, 1992 LETCHWORTH GB, pages 980-2, G.-Z. WANG ET AL. 'Ruthenium-catalysed transfer hydrogenation of imines by propan-2-ol' see table1, compounds 1-4, 9, ---	1,17
X	TETRAHEDRON: ASYMMETRY, vol. 2, no. 3, 1991 OXFORD GB, pages 183-186, S. G. DAVIES ET AL. 'Asymmetric synthesis of R-.beta.-amino butanoic acid and S-.beta.tyrosine' see page 184, compounds 3,4,5 --- -/--	1,17

2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/13704

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAN. J. CHEM. (1994), 72(7), 1699-704 , July 1994 MAJEWSKI, MAREK ET AL. 'Enantioselective deprotonation of protected 4-hydroxycyclohexanones' see page 1700, compounds 6,5,4, left column, line 1 - line 8; see page 1702, right column, last paragraph - page 1703, left column, line 14	1,17
X	TETRAHEDRON, vol. 41, no. 24, 1985 OXFORD GB, pages 6005-11, J. C. G. VAN NIEL ET AL. 'NADH models XXI. Stereoselective reduction of chireal imines with hantzsch ester' see compounds 5a-e, 6a-e	1,17
X	US,A,4 000 197 (FREEDMAN HAROLD H ET AL) 8 February 1977 see table I, examples 1,3,5,7,9,11,13	1
X	DE,B,12 31 690 (SANDOZ) 12 December 1967 see examples 2A,3A	17
P,X	WO,A,95 11221 (NPS PHARMA INC ;NEMETH EDWARD F (US); WAGENEN BRADFORD C VAN (US);) 27 April 1995 see page 9/1, line 5 - line 11; claims see figures	1-13, 16-21
P,X	WO,A,95 21815 (ABBOTT LABORATORIES, USA) 17 August 1995 see RN 171349-82-9, 1-Naphthalenemethanamine, .alpha.-methyl-N-[(4-phenoxyphenyl)methyl] -	1,5,6
P,X	WO,A,95 18134 (OXFORD ASYMMETRY LTD ;DAVIES STEPHEN GRAHAM (GB); POLYWKA MARIO EU) 6 July 1995 see page 14, preparation 3 and page 4, compound (4)	16
P,X	SYNLETT, no. 9, 1995 STUTTGART DE, pages 961-2, YUKIHIKO HASHIMOTO ET AL. 'Highly diastereoselective addition of organometallic reagents to chiral imines derived from 1-(2-methoxyphenyl)ethylamine' see table 1, compounds 1,7,8,9	1,16,17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/13704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Please see attached sheet ./.

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

Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US95/ 13704

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Remark: Although claims 19-21 are directed to a method of treatment of the human body the search has been carrried out and based on the alleged effects of the compounds and/or compositions

The search for the compounds according to claims 1, 16 and 17 has been carried out completely , but revealed too many pertinent documents and/or compounds, which for economical reasons can not all be cited. Therefore the search report should not be considered complete for all the claims. The report is complete for the (R)- and (R,R) enantiomers of claim 3-7, 9, 10, 12-15 and for compounds according to claim 16.
The search report is also complete for all compounds used as calcium (ion) receptor modulators.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/13704

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9418959	01-09-94	AU-B-	3777093	14-09-94
		EP-A-	0637237	08-02-95
		JP-T-	7506380	13-07-95
WO-A-9304373	04-03-93	AU-B-	2588992	16-03-93
		CA-A-	2115828	04-03-93
		EP-A-	0657029	14-06-95
		JP-T-	6510531	24-11-94
		NO-A-	940581	25-04-94
		WO-A-	9511221	27-04-95
		ZA-A-	9206360	30-03-93
EP-A-0508307	14-10-92	CA-A-	2065476	09-10-92
		DE-D-	69206306	11-01-96
		JP-A-	5201938	10-08-93
		US-A-	5298660	29-03-94
DE-A-2541184	15-04-76	AR-A-	210586	31-08-77
		AR-A-	211558	30-01-78
		AT-B-	343101	10-05-78
		AT-B-	337675	11-07-77
		AU-B-	497358	07-12-78
		AU-B-	8495675	24-03-77
		BE-A-	833824	16-01-76
		CH-A-	609323	28-02-79
		CH-A-	596139	28-02-78
		FR-A,B	2285865	23-04-76
		GB-A-	1464209	09-02-77
		JP-A-	51059843	25-05-76
		NL-A-	7511183	29-03-76
		SE-A-	7510611	26-03-76
US-A-4000197	28-12-76	NONE		
DE-B-1231690		FR-M-	4380	
		FR-A-	1451245	03-12-66
		GB-A-	1087601	
		US-A-	3318952	09-05-67
WO-A-9511221	27-04-95	AU-B-	2588992	16-03-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/13704

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9511221		CA-A-	2115828	04-03-93
		EP-A-	0657029	14-06-95
		JP-T-	6510531	24-11-94
		NO-A-	940581	25-04-94
		WO-A-	9304373	04-03-93
		ZA-A-	9206360	30-03-93
		AU-B-	8087294	08-05-95
WO-A-9521815	17-08-95	NONE		
WO-A-9518134	06-07-95	NONE		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(22) International Filing Date: 30 April 1997 (30.04.97)

(30) Priority Data:
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(54) Title: INORGANIC ION RECEPTOR-ACTIVE COMPOUNDS

(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 using such compounds. Preferred compounds can mimic or block the effect of extracellular calcium on a cell surface calcium receptor.

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DESCRIPTION

Inorganic Ion Receptor-Active Compounds

FIELD OF THE INVENTION

This invention relates to compounds able to modulate one or more inorganic ion receptor activities.

BACKGROUND OF THE INVENTION

The references provided herein are not admitted to be prior art to the claimed invention.

Certain cells in the body respond not only to chemical signals, but also to ions such as extracellular calcium ions (Ca^{2+}). Extracellular Ca^{2+} is under tight homeostatic control and regulates various processes such as blood clotting, nerve and muscle excitability, and proper bone formation.

Calcium receptor proteins enable certain specialized cells to respond to changes in extracellular Ca^{2+} concentration. For example, extracellular Ca^{2+} inhibits the secretion of parathyroid hormone (PTH) from parathyroid cells, inhibits bone resorption by osteoclasts, and stimulates secretion of calcitonin from C-cells.

PTH is the principal endocrine factor regulating Ca^{2+} homeostasis in the blood and extracellular fluids. PTH, by acting on bone and kidney cells, increases the level of Ca^{2+} in the blood. This increase in extracellular Ca^{2+} then acts as a negative feedback signal, depressing PTH secretion. The reciprocal relationship between extracellular Ca^{2+} and PTH secretion forms an important mechanism maintaining bodily Ca^{2+} homeostasis.

Extracellular Ca^{2+} acts directly on parathyroid cells to regulate PTH secretion. The existence of a parathyroid cell surface protein which detects changes in extracellular Ca^{2+} has been confirmed. (Brown *et al.*, *Nature* *366*:574, 1993.)

In parathyroid cells, this protein, the calcium receptor, acts as a receptor for extracellular Ca^{2+}, detects changes in the ion concentration of extracellular Ca^{2+}, and initiates a functional cellular response, PTH secretion.

Extracellular Ca^{2+} can exert effects on different cell functions, reviewed in Nemeth *et al.*, *Cell Calcium 11*:319, 1990. The role of extracellular Ca^{2+} in parafollicular (C-cells) and parathyroid cells is discussed in Nemeth, *Cell Calcium 11*:323, 1990. These cells were shown to express similar calcium receptors. (See Brown *et al.*, *Nature 366*:574, 1993; Mithal *et al.*, *J. Bone Miner. Res. 9*, Suppl. 1, s282, 1994; Rogers *et al.*, *J. Bone Miner. Res. 9*, Suppl, 1, s409, 1994; Garrett *et al.*, *Endocrinology 136*:5202-5211, 1995.)

The ability of various molecules to mimic extracellular Ca^{2+} *in vitro* is discussed in references such as Nemeth *et al.*, in "Calcium-Binding Proteins in Health and Disease," 1987, Academic Press, Inc., pp. 33-35; Brown *et al.*, *Endocrinology 128*:3047, 1991; Chen *et al.*, *J. Bone Miner. Res. 5*:581, 1990; and Zaidi *et al.*, *Biochem. Biophys. Res. Commun. 167*:807, 1990.

Nemeth *et al.*, PCT/US92/07175, International Publication Number WO 93/04373, Nemeth *et al.*, PCT/US93/01642, International Publication Number WO 94/18959, and Nemeth *et al.*, PCT/US94/12117, International Publication Number WO 95/11211, describe various compounds which can modulate the effect of an inorganic ion receptor.

SUMMARY OF THE INVENTION

The present invention features compounds able to modulate one or more activities of an inorganic ion receptor and methods for treating diseases or disorders using such

compounds. Preferred compounds can mimic or block the effect of extracellular calcium on a cell surface calcium receptor.

Inorganic ion receptor activities are those processes brought about as a result of inorganic ion receptor activation. Such processes include the production of molecules which can act as intracellular or extracellular messengers.

Inorganic ion receptor-modulating compounds include ionomimetics, ionolytics, calcimimetics, and calcilytics. Ionomimetics are compounds which mimic (*i.e.*, evoke or potentiate) the effects of an inorganic ion at an inorganic ion receptor. Preferably, the compound affects one or more calcium receptor activities. Calcimimetics are ionomimetics which affect one or more calcium receptor activities.

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

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

A measure of the effectiveness of a compound to modulate receptor activity can be determined by calculating the EC_{50} or IC_{50} for that compound. The EC_{50} is the concentration of a compound which causes a half-maximal mimicking effect. The

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

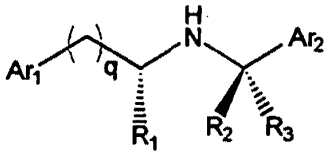
An inorganic ion receptor-modulating compound preferably selectively targets inorganic ion receptor activity in a particular cell. For example, selective targeting of a calcium receptor activity is achieved by a compound exerting a greater effect on a calcium receptor activity in one cell type than at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

Preferably, the compound is either a calcimimetic or calcilytic having an EC_{50} or an IC_{50} at a calcium receptor of

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

Thus, a first aspect the invention features an inorganic ion receptor-modulating compound having the formula:

STRUCTURE I



wherein Ar_1 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted heterocyclic aryl, where up to 5 substituents may be present and each substituent is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, $N(alkyl)_2$, phenyl, phenoxy, benzyl, benzyloxy, α,α-dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, acetyl, OCH_2COOH, and ethylene dioxy;

Ar_2 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted

heterocyclic aryl, where up to 5 substituents may be present and each substituent is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, OCH_2COOH, ethylene dioxy, and acetoxy;

q is 0, 1, 2, or 3;

R_1 is either H or alkyl; and

R_2 and R_3 are each independently either hydrogen, alkyl, or together cycloalkyl or cycloalkenyl;

and pharmaceutically acceptable salts and complexes thereof.

Preferably, the compound is an ionomimetic which modulates one or more inorganic ion receptor activities, more preferably the compound is a calcimimetic.

"Alkenyl" refers to a hydrocarbon chain having 2-6 carbons and at least one double-bond which may be a straight chain, branched, or non-aromatic cyclic. Preferably, the alkenyl has 2-4 carbon atoms.

"Alkyl" refers to a saturated hydrocarbon having 1-6 carbons which may be a straight chain, branched, or cyclic. Preferably, the alkyl has 1-4 carbon atoms.

"Alkoxy" refers to "O-alkyl," where "O" is an oxygen joined to an alkyl.

"Cycloalkenyl" refers to a non-aromatic cyclic hydrocarbon chain having 3-12 carbons and at least one double-bond, and includes multiple ring structures. Preferably, the cycloalkenyl has 3 to 6 carbon atoms.

"Cycloalkyl" refers to a saturated cyclic hydrocarbon chain having 3-12 carbons, and includes multiple ring structures. Preferably, the cycloalkyl has 3 to 6 carbon atoms.

"Thioalkyl" refers to "S-alkyl," where "S" is a sulfur joined to an alkyl.

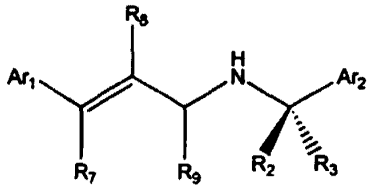
"Haloalkyl" refers to an alkyl substituted with at least one halogen. Preferably, only the terminal carbon of the haloalkyl is substituted with a halogen and 1 to 3 halogens are present. More preferably, the haloalkyl contains 1 carbon. Preferably, the halogen substitutions are either Cl or F.

"Haloalkoxy" refers to "O-haloalkyl," where "O" is an oxygen joined to a haloalkyl.

"Heterocyclic aryl" refers to an aryl ring system having 1 to 3 heteroatoms as ring atoms in a heteroaromatic ring system and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Preferably, the heterocyclic ring system is mono- or bicyclic. More preferably, the heterocyclic aryl is either furanyl, thiofuranyl (also known as "thienyl"), benzofuranyl or benzothiofuranyl (also known as "benzothienyl").

Another aspect of the present invention features an inorganic ion receptor-modulating compound having the formula:

STRUCTURE II



Where Ar_1, Ar_2, R_2 and R_3 are as described for Structure I compounds;

R_7 is either hydrogen, alkyl or phenyl;

R_8 is either hydrogen, or alkyl;

R_9 is either hydrogen, alkyl or phenyl;

and pharmaceutically acceptable salts and complexes thereof.

Preferably, the compound is an ionomimetic modulating one or more inorganic ion receptor activities, more preferably the compound is a calcimimetic.

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

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

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

Another aspect the present invention features a method for treating a patient by using inorganic ion receptor-modulating compounds described herein. The method involves administering to the patient a pharmaceutical composition containing a therapeutically effective amount of an inorganic ion receptor-modulating compound. In a preferred embodiment,

the disease or disorder is treated by administering to the patient a therapeutically effective amount of a calcium receptor-modulating compound.

Inorganic ion receptor-modulating compounds, and compositions containing such compounds, can be used to treat different types of patients. A "patient" refers to a mammal in which compounds able to modulate inorganic ion receptor activity will have a beneficial effect including a beneficial prophylactic effect. Suitable patients can be diagnosed using standard techniques known to those in the medical profession.

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

Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, osteoporosis and other bone and mineral-related disorders, and the like (as described, *e.g.*, in standard medical text books, such as "Harrison's Principles of Internal Medicine"). Such diseases are treated using calcium receptor-modulating compounds which mimic or block one or more of the effects of extracellular Ca^{2+} on a calcium receptor.

By "therapeutically effective amount" is meant an amount of a compound which relieves to some extent one or more symptoms of a disease or disorder in the patient; or returns

to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of the disease or disorder. Thus, a therapeutically effective amount can be an amount effective to prophylactically decrease the likelihood of the onset of a disease or disorder.

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

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

In a preferred embodiment, the compound reduces the level of parathyroid hormone in the serum of the patient. More preferably, the level is reduced to a degree sufficient

to cause a decrease in plasma Ca^{2+}. Most preferably, the parathyroid hormone level is reduced to that present in a normal individual.

Patients in need of treatment using the compounds described by the present invention can be diagnosed by standard medical techniques, such as blood or urine analysis. Examples of such medical techniques include detecting a deficiency of protein whose production or secretion is affected by changes in inorganic ion concentrations, and by detecting abnormal levels of inorganic ions or hormones which effect inorganic ion homeostasis.

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

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

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 provides the chemical structures of different ionomimetic compounds.

Figure 2 provides the chemical structures of different ionomimetic compounds.

Figure 3 provides the chemical structures of different ionomimetic compounds.

Figure 4 provides the chemical structures of different ionomimetic compounds.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention features compounds able to modulate one or more inorganic ion receptor activities. Preferably, the compounds can mimic or block an effect of an

extracellular ion on a cell having an inorganic ion receptor, more preferably, the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor. Most preferably, the compounds can mimic the effect of extracellular Ca^{2+} on a cell having a calcium receptor.

While the compounds described herein are believed to be able to act at an inorganic ion receptor, preferably a calcium receptor, unless otherwise explicitly stated in the claims that a compound exerts an effect by acting at a receptor, there is no intention to limit the claimed methods to those requiring modulation of receptor activity. Rather, the compounds are characterized by their ability to modulate inorganic ion receptor activity *in vivo* or *in vitro*.

I. CALCIUM RECEPTORS

Calcium receptors are present in different cells. The pharmacological effects of the following cells, in response to extracellular Ca^{2+}, is consistent with the presence of a calcium receptor: parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, trophoblast in the placenta, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, endocrine and exocrine cells in the pancreas, fat/adipose cell, immune cell, GI tract cell, skin cell, adrenal cell, pituitary cell, hypothalamic cell, and cell of the subfornical organ.

The presence of a calcium receptor on the following cells have been confirmed using physical data, such as hybridization with nucleic acid encoding a calcium receptor: parathyroid cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct in the kidney, parafollicular cell in the thyroid (C-cell), intestinal cell, GI tract cell, pituitary cell, hypothalamic cell, cell of the subfornical organ, and endocrine and exocrine cells in the pancreas.

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

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

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

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

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

(a) A rapid (time to peak < 5 seconds) and transient increase in $[Ca^{2+}]_i$ that is refractory to inhibition by 1 μM La^{3+} or 1 μM Gd^{3+} and is abolished by pretreatment with ionomycin (in the absence of extracellular Ca^{2+});

(b) The increase is not inhibited by dihydropyridines;

(c) The transient increase is abolished by pretreatment for 10 minutes with 10 mM sodium fluoride;

(d) The transient increase is diminished by pretreatment with an activator of protein kinase C (PKC), such as phorbol myristate acetate (PMA), mezerein or (-)-indolactam V. The overall effect of the protein kinase C activator is to shift the concentration-response curve of calcium to the right without affecting the maximal response; and

(e) Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect the increase.

2. A rapid (< 30 seconds) increase in the formation of inositol-1,4,5-triphosphate or diacylglycerol. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect this increase;

3. The inhibition of dopamine- and isoproterenol-stimulated cyclic AMP formation. This effect is blocked by pretreatment with pertussis toxin (100 ng/ml for > 4 hours); and

4. The inhibition of PTH secretion. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect the inhibition in PTH secretion.

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

II. INORGANIC ION RECEPTOR-MODULATING COMPOUNDS

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

A preferred method of measuring calcium receptor activity is to measure changes in $[Ca^{2+}]_i$. Changes in $[Ca^{2+}]_i$ can be measured using different techniques such as by using

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

In a preferred embodiment, the compound has an EC_{50} or IC_{50} less than or equal to 5 μM at one or more, but not all cells chosen from the group consisting of: parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell, GI tract cell, skin

cell, adrenal cell, pituitary cell, hypothalamic cell, and cell of the subfornical organ. More preferably, the cells are chosen from the group consisting of parathyroid cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct in the kidney, parafollicular cell in the thyroid (C-cell), intestinal cell, GI tract cell, pituitary cell, hypothalamic cell, and cell of the subfornical organ. The presence of a calcium receptor in this group of cells has been confirmed by physical data such as *in situ* hybridization and antibody staining.

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

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

Inorganic receptor-modulating compounds need not effect inorganic receptor activity to the same extent or in exactly

the same manner as the natural ligand. For example, a calcimimetic may affect calcium receptor activity to a different extent, to a different duration, by binding to a different binding site, or by having a different affinity, compared to calcium acting at a calcium receptor.

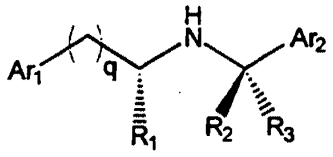
A. Ionomimetics

Different compound are described by Nemeth *et al.*, PCT/US92/07175, International Publication Number WO 93/04373, Nemeth *et al.*, PCT/US93/01642, International Publication Number WO 94/18959, Nemeth *et al.*, PCT/US94/12117, International Publication Number WO 95/11211, and Van Wagenen *et al.* PCT/US95/13704 (each of these references are hereby incorporated by reference herein). Different generic groups are described herein, preferably, these groups exclude each of the specific compounds described in these prior international applications (*i.e.*, the specific compounds described in PCT/US92/07175, PCT/US93/01642, PCT/US94/12117, and PCT/US95/13704, are preferably excluded from the different generic and subgeneric formula provided herein).

1. Structure I Compounds

Structure I compounds able to modulate calcium receptor activity have the following formula:

STRUCTURE I



Where Ar_1 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted heterocyclic aryl, where up to 5 substituents may be present and each substituent is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, $N(alkyl)_2$, phenyl, phenoxy, benzyl, benzyloxy, α,α-dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, acetyl, OCH_2COOH, and ethylene dioxy. In one embodiment of the present invention Ar_1 is either an optionally substituted naphthyl, or a substituted phenyl, having 1 to 4 substituents, more preferably Ar_1 is either an unsubstituted naphthyl or a substituted phenyl; more preferably, Ar_1 is a substituted phenyl; preferably each Ar_1 substituent is independently selected from the group consisting of: isopropyl, CH_3O, CF_3 CH_3S, CF_3O, Br, I, Cl, F, and CH_3. In another embodiment of the present invention Ar_1 is an optionally substituted heterocyclic aryl. Preferred heterocyclic aryl substituents are independently selected from the group consisting of: isopropyl, CH_3O, CF_3 CH_3S, CF_3O, Br, I, Cl, F, and CH_3. Preferred heterocyclic aryls are either furanyl, thiofuranyl, benzofuranyl, or benzothiophenyl;

Ar_2 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted heterocyclic aryl, where up to 5 substituents may be present and each substituent is independently selected from the group

consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, OCH_2COOH, ethylene dioxy, and acetoxy; In one embodiment Ar_2 is preferably either an optionally substituted naphthyl, or a substituted phenyl having 1 to 4 substituents, more preferably Ar_2 is either an unsubstituted naphthyl or a substituted phenyl; more preferably, Ar_2 is a substituted phenyl with a substituent in the *meta* position, even more preferably, Ar_2 is mono substituted with a substituent in the *meta* position; preferably each Ar_2 substituent is independently selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3, more preferably a CH_3O is located in the *meta* position. In another embodiment of the present invention Ar_2 is an optionally substituted heterocyclic aryl. Preferred heterocyclic aryl substituents are independently selected from the group consisting of: isopropyl, CH_3O, CF_3 CH_3S, CF_3O, Br, I, Cl, F, and CH_3. Preferred heterocyclic aryls are either furanyl, thiofuranyl, benzofuranyl, or benzothiophenyl;

q is 0, 1, 2, or 3; in alternative embodiments q is 0 or 2;

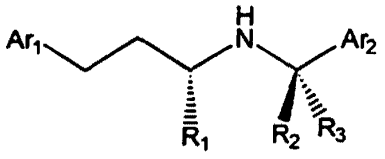
R_1 is either H or alkyl; when R_1 is alkyl in alternative embodiments the alkyl is methyl, or the alkyl has more than one carbon atom, preferably 2 to 4 carbon atoms;

R_2 and R_3 are each independently either hydrogen, alkyl, or together cycloalkyl or cycloalkenyl; preferably, R_2 and R_3 are each independently either hydrogen or alkyl, provided that at least one of R_2 and R_3 is not hydrogen, preferably, R_2 is alkyl, more preferably R_2 is methyl;

and pharmaceutically acceptable salts and complexes thereof.

In a more preferred embodiment the compound has following formula:

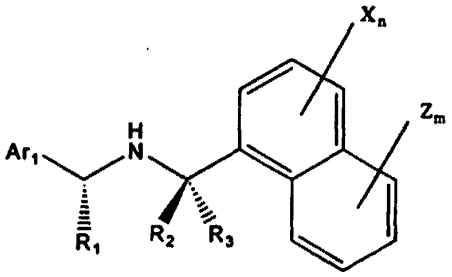
STRUCTURE IA



Where Ar_1, Ar_2, R_1, R_2, and R_3 are as described above for Structure I compounds, including preferred embodiments.

In another more preferred embodiment the compound has the formula:

Structure IB



Where Ar_1, R_1, R_2, and R_3 is as described above for Structure I compounds including preferred embodiments;

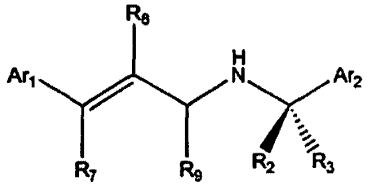
each X and Z is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, OCH_2COOH, ethylene dioxy, and acetoxy; more preferably each X and Z is independently selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3;

n and m are each independently 0, 1, 2, or 3, provided that n and m together are no more than 5; preferably n and m are each independently 0 or 1, more preferably, 0.

2. Structure II Compounds

Structure II compounds have the formula:

STRUCTURE II



Where Ar_1, Ar_2, R_3 and R_4 are as described above for Structure I compounds, including preferred embodiments;

R_7 is either hydrogen, alkyl or phenyl; preferably hydrogen;

R_8 is either hydrogen, or alkyl; preferably hydrogen;

R_9 is either hydrogen, alkyl or phenyl; preferably hydrogen or alkyl, when R_9 is alkyl in alternative embodiments the alkyl is methyl, or the alkyl has more than one carbon atom, preferably 2 to 4 carbon atoms;

and pharmaceutically acceptable salts and complexes thereof.

3. Calcimimetic Activity

The ability of compounds to mimic the activity of Ca^{2+} at calcium receptors can be determined using procedures known in the art such as those described by Nemeth *et al.*, PCT/US93/01642, International Publication Number WO 94/18959. For example, calcimimetics possess one or more and preferably

all of the following activities when tested on parathyroid cells *in vitro*:

1. The compound causes a rapid (time to peak < 5 seconds) and transient increase in intracellular calcium concentration that is refractory to inhibition by 1 μM La^{3+} or 1 μM Gd^{3+}. The increase in $[Ca^{2+}]_i$ persists in the absence of extracellular Ca^{2+}, but is abolished by pretreatment with ionomycin (in the absence of extracellular Ca^{2+});

2. The compound potentiates increases in $[Ca^{2+}]_i$ elicited by submaximal concentrations of extracellular Ca^{2+};

3. The increase in $[Ca^{2+}]_i$ elicited by extracellular Ca^{2+} is not inhibited by dihydropyridines;

4. The transient increase in $[Ca^{2+}]_i$ caused by the compound is abolished by pretreatment for 10 minutes with 10 mM sodium fluoride;

5. The transient increase in $[Ca^{2+}]_i$ caused by the compound is diminished by pretreatment with an activator of protein kinase C (PKC), such as phorbol myristate acetate (PMA), mezerein or (-)-indolactam V. The overall effect of the protein kinase C activator is to shift the concentration-response curve of the compound to the right without affecting the maximal response;

6. The compound causes a rapid (< 30 seconds) increase in the formation of inositol-1,4,5-triphosphate and/or diacylglycerol;

7. The compound inhibits dopamine- or isoproterenol-stimulated cyclic AMP formation;

8. The compound inhibits PTH secretion;

9. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) blocks the inhibitory effect of the compound on cyclic AMP formation, but does not effect increases in

$[Ca^{2+}]_i$, inositol-1,4,5-triphosphate, or diacylglycerol, nor decreases in PTH secretion;

10. The compound elicits increases in Cl^- current in *Xenopus* oocytes injected with poly(A)$^+$-enriched mRNA from bovine or human parathyroid cells, but is without effect in *Xenopus* oocytes injected with water, or liver mRNA; and

11. Similarly, using a cloned calcium receptor from a parathyroid cell, the compound will elicit a response in *Xenopus* oocytes injected with the specific cDNA or mRNA encoding the receptor.

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

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

The transient increase in $[Ca^{2+}]_i$ is preferably abolished by pretreatment of the cell for ten minutes with 10 mM sodium fluoride, or the transient increase is diminished by brief

pretreatment (not more than ten minutes) of the cell with an activator of protein kinase C, preferably, phorbol myristate acetate (PMA), mezerein or (-) indolactam V.

B. Calcilytics

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

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

(a) increase $[Ca^{2+}]_i$,

(b) mobilize intracellular Ca^{2+},

(c) increase the formation of inositol-1,4,5-triphosphate,

(d) decrease dopamine- or isoproterenol-stimulated cyclic AMP formation, and

(e) inhibit PTH secretion;

2. The compound blocks increases in Cl^- current in *Xenopus* oocytes injected with poly(A)$^+$-mRNA from bovine or human parathyroid cells elicited by extracellular Ca^{2+} or calcimimetic compounds, but not in *Xenopus* oocytes injected with water or liver mRNA;

3. Similarly, using a cloned calcium receptor from a parathyroid cell, the compound will block a response in *Xenopus* oocytes injected with the specific cDNA, mRNA or

cRNA encoding the calcium receptor, elicited by extracellular Ca^{2+} or a calcimimetic compound.

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

III. TREATMENT OF DISEASES OR DISORDERS

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

Examples of intracellular messengers include cAMP, cGMP, IP_3, and diacylglycerol.

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

Diseases and disorders characterized by abnormal calcium homeostasis can be due to different cellular defects such as a defective calcium receptor activity, a defective number of calcium receptors, or a defective intracellular protein acted on by a calcium receptor. For example, in parathyroid cells, the calcium receptor is coupled to the G_i protein which in turn inhibits cyclic AMP production. Defects in G_i protein can affect its ability to inhibit cyclic AMP production.

Diseases or disorders which can be treated by modulating calcium receptor activity are known in the art. For example, diseases or disorders which can be treated by modulating calcium receptor activity can be identified based on the functional responses of cells regulated by calcium receptor activity.

Functional responses of cells regulated by calcium receptor are know in the art, including PTH secretion by parathyroid cells, calcitonin secretion by C-cells, and bone resorption by osteoclasts. Such functional responses are associated with different diseases or disorders. For example, hyperparathyroidism results in elevated levels of PTH in the plasma. Decreasing the plasma levels of PTH offers an effective means of treating hyperparathyroidism. Likewise, increasing plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for osteoporosis. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and osteoporosis.

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

All three of these approaches will result in beneficial effects to patients suffering from osteoporosis.

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

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

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

extracellular Ca^{2+}-induced increases in $[Ca^{2+}]_i$ is shifted to the right and the magnitude of such increases is reduced.

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

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

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

Isolated osteoclasts respond to increases in the concentration of extracellular Ca^{2+} with corresponding increases in $[Ca^{2+}]_i$ that arise partly from the mobilization of intracellular Ca^{2+}. Increases in $[Ca^{2+}]_i$ in osteoclasts are

associated with the inhibition of bone resorption. Release of alkaline phosphatase from bone-forming osteoblasts is directly stimulated by calcium.

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

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

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

Specific diseases and disorders which might be treated or prevented, based upon the affected cells, also include

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

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

IV. ADMINISTRATION

The compounds described by the present invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co., Easton, PA, 1990 (hereby incorporated by reference herein).

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

Compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include an 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate:diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and

quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol, are present. For example, see Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co., Easton, PA, p. 1445, 1990. Such salts can be prepared using the appropriate corresponding bases.

Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound is dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol in solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt is prepared by reacting the free base and acid in an organic solvent. (See, *e.g.*, PCT/US92/03736, hereby incorporated by reference herein.)

Carriers or excipients can also be used to facilitate administration of the compound. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of

physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution and dextrose.

The compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, for example, intramuscular, intravenous, intraperitoneal, and/or subcutaneous administration. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, buccal or sublingual tablets, rectal suppositories, or vaginal suppositories.

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

The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, EC_{50}, the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art. Generally, it is an amount between about 0.01 and 50 mg/kg, preferably 0.01 and 20 mg/kg of the animal to be treated.

V. EXAMPLES

Examples are provided below illustrating different aspects and embodiments of the present invention. These examples are not intended to limit the claimed invention. Included in these examples are synthesis protocols illustrating techniques which can be used to synthesize different compounds described herein. Other compounds falling within the generic groups described herein can be prepared using standard techniques.

Example 1. Assaying Calcium Receptor Activity

The ability of different compounds to modulate calcium receptor activity are described in this example. Other methods which can be used to measure calcium receptor activity are known in the art.

Recombinant HEK 293 4.0-7 cells containing a calcium receptor were constructed as described by Rogers *et al.*, *J. Bone Miner. Res. 10* Suppl. 1:S483, 1995 (hereby incorporated by reference herein). The recombinant cells were loaded with

fura-2 by incubating the cells in Dulbecco's modified Eagle's medium buffered with 20 mM HEPES containing about 5 μM fluo-3/AM for one hour at room temperature. Cells were then rinsed with Hank's balanced salt solution buffered with 20 mM HEPES containing 1 mM $CaCl_2$ and 1 mM $MgCl_2$. Compounds to be tested were then added to the cells and fluorescence was measured (excitation and emission wavelengths of 340 and 510 nm, respectively). Table I provides results for different compounds.

Table I

Compound	EC_{50} (nM)
26A	52 (1)
6X	286
26B	10900
26C	22000
26D	47 (3)
26E	77 (3)
26F	15 (3)
26G	11 (3)
26H	36 (1)
26I	126 (1)
26J	47 (1)
27E	12000
27F	230
27G	70
27H	2750
28O	2500
27J	1100
27K	3800
27L	>100000
27M	1800
27N	960
27O	29
27P	1600
27Q	23
27R	2550
27S	210
27T	2900
27U	210

Compound	EC_{50} (nM)
27V	140
27W	1500
27X	22
27Y	12
27Z	16
28A	9.5
28B	24
28C	270
28D	7300
28E	810
28F	660
28G	602
28H	3000
28I	1200
28J	1100
28K	57
28L	> 3000
28M	170
28N	303

Example 2: Synthesis of 26D. (*R,R*)-*N*-(1-Ethyl-4'-iodophenyl)-1-(1-naphthyl)ethylamine hydrochloride

The synthesis of the title compound (26D) was accomplished in a one-pot, two-step reaction sequence by reductive amination of the imine formed from the commercially available 4'-iodoacetophenone and (*R*)-naphthyl-1-ethylamine. The reduction of the imine diastereoselectively was conducted under similar conditions as previously reported (*Tetrahedron Lett.* (1985) 41, 6005-6011.).

A mixture of 4'-iodoacetophenone (0.25 g, 1.0 mmol), (*R*)-naphthyl-1-ethylamine (0.17 g, 1.0 mmol), and $Ti(i\text{-}PrO)_4$ (0.38 mL, 1.1 mmol) in abs. EtOH (5 mL) was refluxed for 18 h. Diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine decarboxylate (0.25 g, 1.0 mmol) and $Mg(ClO_4)_2$ (0.22 g, 1.0 mmol) were then added to the reaction mixture and the reflux was continued for an additional 18 h. The reaction mixture was then cooled to

ambient temperature, H_2O (3 mL) and diethyl ether (10 mL) were added and the mixture was centrifuged (3000 rpm) to remove the inorganic salts. The supernatant was decanted away from the pellet and the volatiles were removed under reduced pressure. The resulting residue was chromatographed on silica gel (elution with 1% MeOH/CH_2Cl_2) to provide the purified product as its free base. This material was converted to its hydrochloride salt. The salt was recrystallized from CH_2Cl_2/hexane to provide GC/MS-pure material.

Example 3: Synthesis of 26E, (*R,R*)-*N*-(1-Ethyl-4'-ethoxy-3'-methylphenyl)-1-(1-naphthyl)ethylamine hydrochloride

The synthesis of the title compound (26E) was accomplished in a three-step, two-pot reaction sequence. Commercially available 4-hydroxy-3-methylacetophenone was *O*-alkylated with ethyl iodide/K_2CO_3/acetone. This ketone was subsequently reacted with (*R*)-naphthyl-1-ethylamine in the presence of Ti(i-PrO)$_4$ to provide the imine. This imine was reduced in high diastereoselective yield by catalytic hydrogenation with Raney-nickel.

A mixture of 4-ethoxy-3-methylacetophenone (2.0 g, 11.2 mmol), (*R*)-naphthyl-1-ethylamine (2.0 g, 11.2 mmol), Ti(i-Pro)$_4$ (4.2 mL, 14.1 mmol), and EtOH (10 mL) were stirred at 60 °C for 18 h. The reaction mixture was then transferred to a Parr hydrogenation flask, Raney-nickel (100 mg; washed with EtOH, 3 x 20 mL) was added, and the mixture was hydrogenated at 50 psig, 25 °C, for 4 h. The reaction mixture was then filtered (Celite/fritted glass), the catalyst was washed (EtOH, 20 mL), and the filtrate was evaporated under reduced pressure to provide the crude product. This material was purified by silica gel chromatography (elution with 2% MeOH/CH_2Cl_2). The free base

was converted to its hydrochloride salt to provide 1.1 g (27%) of a white solid.

Example 4: Synthesis of 26F. (*R,R*)-*N*-(1-Propyl-4'-methoxy-3'-methylphenyl)-1-(1-naphthyl)ethylamine hydrochloride

The synthesis of the title compound (26F) was accomplished in a four-step, three-pot reaction sequence. Commercially available 3-methyl-*p*-anisaldehyde was reacted with ethylmagnesium bromide to provide its phenylpropanol derivative. This alcohol was then oxidized to the corresponding ketone in the usual manner with PCC. This ketone was subsequently reacted with (*R*)-naphthyl-1-ethylamine in the presence of $Ti(i\text{-}PrO)_4$ to provide the imine. This imine was reduced in high diastereoselective yield by catalytic hydrogenation in the presence of Raney-nickel.

In a manner similar to the synthesis of 26E, a mixture of 4-methoxy-3-methylpropiophenone (5.7 g, 31.7 mmol), (*R*)-naphthyl-1-ethylamine (5.2 mL, 31.7 mmol), $Ti(i\text{-}Pro)_4$ (11.8 mL, 39.6 mmol), and EtOH (30 mL) were reacted as above to form the imine which was subsequently reduced under catalytic hydrogenation conditions over Raney-nickel. The crude product was purified by silica gel chromatography (elution with 10:1, hexane/EtOAc). The free base was converted to its hydrochloride salt to provide 0.50 g (4%) of a white solid.

Example 5: Synthesis of 26G. (*R,R*)-*N*-(1-Ethyl-4'-methoxy-3'-bromophenyl)-1-(1-naphthyl)ethylamine hydrochloride

The synthesis of the title compound (26G) was accomplished in a four-step, three-pot reaction sequence. Commercially available 3-bromo-4-methoxybenzaldehyde was reacted with methylmagnesium bromide to provide its phenylethanol derivative. This alcohol was then oxidized to the corresponding ketone in

the usual manner with pyridinium chlorochromate (PCC). This ketone was subsequently reacted with (*R*)-naphthyl-1-ethylamine in the presence of Ti(i-PrO)$_4$ to provide the imine. This imine was reduced in high diastereoselective yield using diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine decarboxylate.

In a manner similar to the synthesis of 26D, a mixture of 3-bromo-4-methoxyacetophenone (3.0 g, 13.1 mmol), (*R*)-naphthyl-1-ethylamine (2.1 mL, 13.1 mmol), and Ti(i-PrO)$_4$ (4.7 mL, 15.7 mmol) in abs. EtOH (100 mL) was reduced with diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine decarboxylate in the presence of $Mg(ClO_4)_2$. The resulting crude material was converted to its hydrochloride salt. The salt was purified by precipitation from diethyl ether/hexane to provide GC/MS-pure material (0.6 g, 11%) as a white solid.

Example 6: Synthesis of 26H, 26I, and 26J. (*R*)-*N*-(3-phenyl-2-propenyl)-1-(1-naphthyl)ethylamine hydrochloride, (*R*)-*N*-(2-methyl-3-phenyl-2-propenyl)-1-(1-naphthyl)ethylamine hydrochloride, and (*R*)-*N*-(2-methoxy-3-phenyl-2-propenyl)-1-(1-naphthyl)ethylamine hydrochloride

The syntheses of the title compounds were accomplished in three, two-step, one-pot reaction sequences. Commercially available cinnamaldehyde, 2-methyl-*trans*-cinnamaldehyde, and 2-methoxycinnamaldehyde, respectively, were reacted with (*R*)-naphthyl-1-ethylamine in the presence of Ti(i-PrO)$_4$ to provide the corresponding imine. These imines were reduced using sodium cyanoborohydride to provide the title compounds in high overall yields.

Example 7: Physical Data

Table II provides physical data for some of the compounds described herein. Gas chromatographic and mass spectral data

were obtained on a Hewlett-Packard 5890 Series II Gas Chromatograph with a 5971 Series Mass Selective Detector [Ultra-2 Ultra Performance Capillary Column (crosslinked 5% Ph Me silicone); column length, 25 m, column i.d., 0.20 mm, film thickness, 0.33 μm; He flow rate, 60 mL/min; injector temp., 250 °C; temp. program, 20 °C/min from 125 to 325 °C for 10 min, then held constant at 325 °C for 6 min].

TABLE II

Compound	GC $_{rt}$	*m/z*
25Z	8.32	285
26A	8.75	286
26B	8.51	288
26C	9.60	346
26D	11.08	401
26E	10.71	333
26F	10.56	333
26G	9.09	385
26H	10.95	287
26I	10.98	301
26J	11.79	317

Additional Gas chromatographic and mass spectral data were obtained on a Hewlett-Packard 5890 Series II Gas Chromatograph with a 5971 Series Mass Selective Detector [Ultra-2 Ultra Performance Capillary Column (crosslinked 5% phenyl methyl silicone); column length, 25 m, column i.d., 0.20 mm; He flow rate, 60 mL/min; injector temp., 250 °C; gradient temperature program, 20 °C/min from 125 to 325 °C for 10 min, then held constant at 325 °C for 6 min].

Compound 26Z, rt = 10.22', m/z (rel. int.) 331 (M+,15), 316 (56), 182 (9), 168 (5), 156 (20), 155 (100), 154 (28), 153

(18), 152 (8), 141 (11), 133 (43), 131 (5), 129 (11), 128 (18), 127 (15), 117 (9), 115 (13), 115 (13), 105 (8), 91 (7).

Compound 27A, rt = 10.13', m/z (rel. int.) 331 (M+,18), 316 (76), 182 (10), 176 (5), 168 (10), 167 (5), 156 (17), 155 (100), 154 (57), 153 (27), 152 (14), 141 (14), 134 (7), 133 (58), 133 (58), 131 (7), 129 (14), 128 (21), 127 (23), 126 (5), 119 (5), 117 (12), 116 (5), 115 (18), 105 (10), 91 (12), 77 (5).

Compound 27D, rt = 9.41', m/z (rel. int.) 292 (M+,5), 171 (7), 160 (7), 157 (9), 147 (6), 146 (9), 145 (66), 143 (7), 134 (7), 133 (20), 132 (11), 131 (13), 129 (10), 119 (11), 117 (25), 116 (100), 115 (14), 115 (14), 105 (10), 103 (5), 91 (16), 89 (17), 77 (8).

Compound 27E, rt = 7.81', m/z (rel. int.) 283 (M+,3), 268 (100), 176 (16), 150 (14), 149 (39), 148 (7), 135 (7), 134 (11), 121 (19), 118 (6), 117 (6), 115 (6), 109 (10), 105 (8), 104 (11), 103 (9), 92 (12), 91 (75), 79 (9), 78 (10), 77 (21), 77 (21), 65 (15), 51 (5), 42 (6), 41 (6).

Compound 27F, rt = 7.38', m/z (rel. int.) 365 (M+,1), 231 (6), 230 (31), 216 (28), 215 (59), 214 (17), 190 (15), 174 (25), 136 (41), 135 (100), 134 (14), 129 (13), 128 (15), 127 (9), 119 (9), 117 (6), 114 (9), 109 (10), 105 (21), 104 (7), 103 (18), 91 (21), 91 (10), 79 (11), 78 (7), 77 (19), 68 (12), 65 (6), 42 (9), 0 (0).

Compound 27G, rt = 7.45', m/z (rel. int.) 365 (M+,4), 231 (8), 230 (49), 216 (44), 215 (86), 213 (27), 190 (23), 187 (6), 175 (6), 174 (31), 136 (37), 135 (100), 134 (14), 130 (8), 129 (11), 128 (13), 127 (9), 120 (7), 120 (7), 116 (5), 115 (8), 109 (8), 105 (19), 103 (13), 92 (8), 91 (16), 79 (8), 77 (13), 68 (9), 0 (0).

Compound 27H, rt = 10.44', m/z (rel. int.) 317 (M+,8), 170 (9), 162 (5), 155 (19), 154 (28), 153 (14), 152 (9), 148 (5),

147 (13), 146 (100), 134 (7), 129 (6), 128 (18), 127 (21), 126 (7), 115 (12), 115 (12), 103 (7), 102 (6), 89 (8), 77 (8).

Compound 27J, rt = 9.88', m/z (rel. int.) 337 (M+,2), 323 (22), 322 (100), 210 (26), 196 (9), 184 (12), 182 (11), 170 (13), 169 (53), 168 (31), 167 (14), 165 (10), 154 (22), 153 (41), 152 (32), 150 (9), 141 (53), 129 (27), 128 (34), 127 (62), 126 (20), 124 (98), 115 (24), 103 (23), 91 (15), 89 (18), 77 (23), 42 (11), 41 (9), 0 (0).

Compound 27K, rt = 9.03', m/z (rel. int.) 342 (M+,.1), 327 (40), 325 (41), 308 (14), 306 (21), 204 (17), 202 (31), 174 (43), 173 (26), 172 (66), 171 (26), 139 (11), 138 (15), 137 (20), 127 (33), 124 (100), 117 (10), 115 (12), 111 (11), 103 (37), 102 (41), 101 (30), 98 (12), 91 (11), 89 (28), 77 (35), 75 (21), 63 (12), 51 (10), 0 (0).

Compound 27L, rt = 8.84', m/z (rel. int.) 264 (M+,24), 145 (100), 145 (7), 119 (29), 118 (26), 118 (16), 117 (7), 116 (5), 102 (37), 92 (10), 91 (41), 90 (41), 77 (6), 76 (9), 75 (14), 75 (14), 65 (5), 64 (21), 63 (23), 51 (8).

Compound 27M, rt = 8.48', m/z (rel. int.) 305 (M+,.0), 291 (6), 290 (31), 164 (28), 136 (17), 135 (100), 120 (6), 111 (7), 111 (7), 105 (16), 103 (9), 98 (7), 92 (6), 91 (13), 79 (8), 77 (12), 65 (5), 63 (5).

Compound 27N, rt = 8.81', m/z (rel. int.) 294 (M+,6), 279 (100), 187 (5), 164 (7), 144 (7), 136 (16), 135 (75), 135 (75), 134 (11), 130 (15), 121 (6), 120 (7), 117 (11), 116 (36), 115 (6), 105 (18), 104 (14), 103 (30), 102 (7), 92 (9), 91 (19), 90 (6), 89 (17), 79 (10), 78 (7), 77 (23), 65 (6), 63 (6).

Compound 27O, rt = 9.33', m/z (rel. int.) 347 (M+,1), 304 (58), 192 (6), 156 (14), 156 (14), 155 (100), 154 (22), 153 (22), 152 (9), 150 (24), 149 (16), 148 (23), 135 (28), 129 (9), 128 (14), 127 (15), 115 (9), 91 (8), 77 (6).

Compound 27P, rt = 9.23', m/z (rel. int.) 347 (M+,.0), 304 (100), 177 (3), 156 (12), 155 (87), 154 (12), 153 (15), 152 (6), 150 (20), 149 (10), 148 (12), 128 (6), 127 (6).

Compound 27Q, rt = 9.64', m/z (rel. int.) 361 (M+,.1), 304 (54), 156 (17), 155 (100), 153 (17), 152 (7), 151 (5), 150 (40), 148 (12), 135 (27), 129 (7), 128 (9), 127 (9), 115 (7), 91 (5), 91 (5).

Compound 27R, rt = 9.16', m/z (rel. int.) 294 (M+,3), 279 (100), 187 (5), 164 (6), 136 (24), 135 (77), 121 (10), 120 (6), 117 (5), 116 (33), 105 (15), 104 (7), 103 (15), 92 (6), 91 (14), 91 (14), 89 (10), 79 (8), 78 (5), 77 (14), 65 (5).

Compound 27S, rt = 9.27', m/z (rel. int.) 338 (M+,.0), 323 (7), 322 (38), 164 (9), 162 (7), 160 (25), 158 (37), 136 (25), 136 (6), 135 (100), 134 (16), 124 (7), 122 (6), 120 (8), 120 (7), 115 (8), 105 (19), 104 (5), 103 (16), 102 (11), 101 (9), 92 (10), 91 (19), 89 (8), 79 (10), 78 (6), 77 (17), 65 (6), 63 (6), 0 (0).

Compound 27U, rt = 8.65', m/z (rel. int.) 385 (M+,3), 230 (16), 230 (16), 216 (12), 215 (55), 214 (15), 210 (12), 174 (19), 156 (23), 155 (100), 154 (27), 153 (24), 152 (12), 140 (5), 129 (15), 128 (25), 127 (22), 126 (5), 115 (12), 109 (5), 68 (5).

Compound 27V, rt = 8.59', m/z (rel. int.) 385 (M+,3), 230 (14), 216 (9), 215 (49), 214 (13), 210 (5), 174 (17), 156 (23), 155 (100), 154 (25), 153 (26), 152 (11), 130 (5), 129 (19), 129 (19), 128 (27), 127 (26), 115 (14), 109 (6), 101 (5), 77 (5), 69 (7).

Compound 27W, rt = 8.88', m/z (rel. int.) 371 (M+,2), 356 (100), 244 (20), 184 (5), 182 (5), 170 (8), 169 (24), 168 (14), 167 (8), 160 (5), 159 (46), 154 (11), 153 (24), 153 (24), 152 (15), 150 (6), 141 (26), 133 (9), 129 (11), 128 (13), 127 (19), 126 (5), 115 (6), 109 (10).

Compound 27X, rt = 10.61', m/z (rel. int.) 419 (M+,.0), 406 (50), 404 (20), 403 (100), 402 (11), 401 (51), 263 (6), 250 (27), 248 (55), 246 (29), 169 (9), 167 (7), 156 (5), 155 (14), 154 (16), 153 (12), 153 (12), 152 (6), 128 (9), 127 (9).

Compound 27Y, rt = 10.21', m/z (rel. int.) 375 (M+,4), 361 (20), 360 (100), 359 (15), 358 (78), 279 (7), 217 (11), 206 (23), 205 (7), 204 (93), 202 (74), 170 (13), 168 (8), 156 (12), 155 (38), 154 (53), 153 (37), 152 (21), 141 (11), 129 (16), 128 (37), 127 (41), 126 (21), 123 (20), 115 (14), 89 (28), 77 (10), 75 (10), 63 (8), 0 (0).

Compound 27Z, rt = 11.10', m/z (rel. int.) 466 (M+,.1), 451 (60), 450 (13), 449 (61), 311 (9), 309 (11), 296 (97), 295 (8), 294 (100), 169 (29), 168 (9), 167 (24), 156 (20), 155 (56), 154 (74), 153 (45), 152 (27), 151 (8), 141 (13), 129 (21), 128 (52), 127 (61), 126 (18), 115 (18), 89 (43), 77 (13), 75 (14), 74 (9), 63 (16), 0 (0).

Compound 28A, rt = 10.73', m/z (rel. int.) 421 (M+,4), 408 (33), 407 (21), 407 (21), 406 (100), 279 (9), 265 (7), 252 (22), 251 (6), 250 (70), 156 (6), 155 (20), 154 (25), 153 (19), 152 (11), 141 (6), 129 (7), 128 (18), 127 (21), 126 (10), 123 (11), 115 (7), 89 (16).

Compound 28B, rt = 10.75', m/z (rel. int.) 417 (M+,3), 274 (5), 261 (16), 261 (16), 247 (10), 246 (100), 156 (7), 155 (29), 154 (35), 153 (19), 152 (11), 141 (6), 129 (8), 128 (23), 127 (23), 126 (7), 115 (8), 105 (9), 91 (7), 90 (16), 89 (9), 77 (15).

Compound 28C, rt = 8.73', m/z (rel. int.) 317 (M+,.1), 303 (12), 302 (62), 282 (9), 178 (6), 149 (22), 148 (100), 148 (7), 135 (9), 131 (6), 127 (16), 124 (46), 119 (12), 117 (6), 115 (8), 104 (6), 103 (24), 102 (6), 92 (9), 91 (65), 90 (7), 89 (18), 78 (6), 77 (25), 65 (19), 63 (11).

Compound 28D, rt = 8.73', m/z (rel. int.) 317 (M+,.1), 303 (14), 302 (71), 282 (11), 178 (6), 149 (23), 149 (23), 148 (100), 135 (9), 131 (6), 127 (14), 124 (42), 119 (10), 117 (5), 115 (7), 103 (19), 92 (8), 91 (56), 90 (5), 89 (14), 78 (6), 77 (19), 65 (16), 63 (7).

Compound 28E, rt = 9.33', m/z (rel. int.) 338 (M+,2), 325 (7), 324 (35), 323 (11), 323 (11), 322 (54), 164 (9), 161 (15), 159 (23), 136 (30), 135 (100), 121 (15), 120 (5), 105 (14), 103 (10), 92 (5), 91 (11), 79 (7), 77 (11).

Compound 28F, rt = 9.11', m/z (rel. int.) 338 (M+,1), 325 (7), 324 (39), 323 (11), 322 (59), 164 (10), 161 (19), 161 (19), 159 (29), 136 (27), 135 (100), 121 (11), 120 (6), 115 (5), 105 (17), 103 (12), 102 (7), 101 (5), 92 (6), 91 (14), 89 (6), 79 (9), 77 (14), 65 (5).

Compound 28G, rt = 7.18', m/z (rel. int.) 251 (M+,6), 236 (43), 156 (6), 155 (26), 154 (32), 153 (24), 152 (18), 152 (18), 151 (6), 141 (8), 129 (11), 128 (25), 127 (31), 126 (11), 115 (12), 95 (12), 82 (6), 81 (100), 77 (8), 53 (27), 51 (6).

Compound 28H, rt = 7.31', m/z (rel. int.) 251 (M+,9), 236 (100), 208 (7), 170 (10), 168 (8), 156 (5), 155 (26), 154 (39), 153 (27), 152 (19), 152 (19), 151 (6), 141 (8), 129 (9), 128 (22), 127 (29), 126 (10), 115 (9), 94 (5), 82 (5), 81 (77), 53 (13).

Compound 28I, rt = 8.20', m/z (rel. int.) 267 (M+,6), 252 (36), 156 (6), 155 (21), 154 (15), 153 (15), 152 (10), 141 (7), 129 (7), 128 (15), 127 (16), 126 (5), 115 (8), 112 (16), 98 (8), 98 (8), 98 (6), 96 (100), 53 (5), 44 (6).

Compound 28J, rt = 8.23', m/z (rel. int.) 267 (M+,6), 251 (56), 170 (11), 155 (25), 154 (31), 153 (23), 153 (23), 152 (16), 151 (5), 141 (7), 129 (9), 128 (22), 127 (26), 126 (9), 115 (10), 111 (7), 110 (7), 98 (6), 97 (8), 96 (100), 85 (5), 77 (5), 53 (6), 44 (9).

Compound 28K, rt = 9.28', m/z (rel. int.) 315 (M+,42), 301 (5), 300 (23), 160 (19), 156 (19), 155 (78), 154 (42), 153 (27), 152 (15), 146 (16), 145 (100), 144 (19), 141 (6), 129 (11), 128 (24), 127 (31), 127 (31), 126 (8), 118 (7), 117 (14), 116 (8), 115 (41), 91 (12), 89 (9), 77 (7).

Compound 28L, rt = 7.41', m/z (rel. int.) 319 (M+,6), 318 (8), 159 (15), 147 (12), 146 (100), 132 (6), 131 (5), 130 (7), 119 (6), 117 (13), 115 (10), 109 (8), 105 (6), 104 (16), 103 (11), 91 (8), 78 (8), 77 (8), 42 (8).

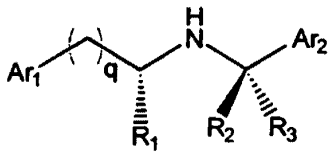
Compound 28M, rt = 10.76', m/z (rel. int.) 372 (M+,2), 360 (8), 359 (10), 358 (44), 357 (16), 356 (68), 169 (6), 168 (29), 167 (8), 160 (32), 158 (51), 156 (17), 155 (100), 154 (29), 153 (34), 152 (18), 151 (6), 141 (9), 129 (18), 128 (25), 127 (28), 126 (8), 124 (7), 122 (9), 115 (19), 102 (6), 101 (7), 89 (10), 77 (7), 0 (0).

Compound 28N, rt = 7.40', m/z (rel. int.) 270 (M+,6), 136 (62), 135 (100), 133 (20), 120 (12), 120 (8), 106 (5), 105 (34), 103 (18), 103 (18), 103 (6), 91 (28), 91 (23), 79 (11), 79 (5), 78 (11), 77 (22), 76 (5), 64 (10), 63 (5), 62 (7).

Other embodiments are within the following claims. Thus, while several embodiments have been shown and described, various modifications may be made without departing from the spirit and scope of the present invention.

Claims

1. An inorganic ion receptor-modulating compound having the formula:



wherein Ar_1 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted heterocyclic aryl, wherein up to 5 substituents may be present and each substituent is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, acetoxy, $N(alkyl)_2$, phenyl, phenoxy, benzyl, benzyloxy, α,α-dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, acetyl, OCH_2COOH, and ethylene dioxy;

Ar_2 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted heterocyclic aryl, wherein up to 5 substituents may be present and each substituent is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, OCH_2COOH, ethylene dioxy, and acetoxy;

q is 0, 1, 2, or 3;

R_1 is either H or alkyl; and

R_2 and R_3 are each independently either hydrogen, alkyl, or together cycloalkyl or cycloalkenyl;

and pharmaceutically acceptable salts and complexes thereof;

wherein said compound is an ionomimetic modulating one or more inorganic ion receptor activities.

2. The compound of claim 1, wherein Ar_1 is said optionally substituted heterocyclic aryl.

3. The compound of claim 2, wherein said Ar_1 optionally substituted heterocyclic aryl is selected from the group consisting of: furanyl, thiofuranyl, benzofuranyl, and benzothiophenyl.

4. The compound of claim 3, wherein

R_2 and R_3 are each independently hydrogen, alkyl, or together either cycloalkyl, provided that at least one of R_2 and R_3 is not hydrogen;

wherein said compound is a calcimimetic modulating one or more calcium receptor activities.

5. The compound of claim 4, wherein R_2 is not hydrogen.

6. The compound of claim 5, wherein R_2 and R_3 are both methyl.

7. The compound of any of claims 1-5, wherein R_3 is hydrogen.

8. The compound of any of claims 1-7, wherein R_1 is alkyl.

9. The compound of claim 8, wherein said R_1 alkyl has more than one carbon atoms.

10. The compound of any of claims 1-7, wherein R_1 is hydrogen.

11. The compound of any of claims 1-10, wherein Ar_2 is a substituted phenyl.

12. The compound of claim 11, wherein said Ar_2 substituted phenyl has one to four independently selected substituents, provided that at least one substituent is located in the *meta* position.

13. The compound of claim 11, wherein said Ar_2 substituted phenyl has 1 to 4 substituents each independently selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3.

14. The compound of claim 11, wherein said Ar_2 substituted phenyl has 1 to 4 substituents each independently selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3, provided that at least one substituent is located in the *meta* position.

15. The compound of any of claims 1-8, wherein Ar_2 is said optionally substituted naphthyl.

16. The compound of claim 15, wherein Ar_2 is an unsubstituted naphthyl.

17. The compound of claim 15, wherein Ar_2 is a substituted naphthyl.

18. The compound of claim 17, wherein said Ar_2 substituted naphthyl has 1 to 4 independently selected substituents.

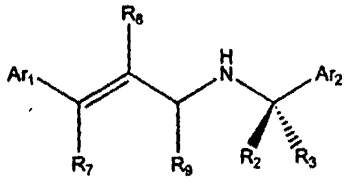
19. The compound of claim 17, wherein said Ar_2 substituted naphthyl has 1 to 4 independently selected substituents selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3.

20. The compound of claim 17, wherein said Ar_2 substituted naphthyl has 1 substituent selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3.

21. The compound of any of claims 1-20, wherein q is 2.

22. The compound of any of claims 1-20, wherein q is 0.

23. An inorganic ion receptor-modulating compound having the formula:



wherein Ar_1 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted heterocyclic aryl, wherein up to 5 substituents may be present and each substituent is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN,

acetoxy, benzyl, benzyloxy, α,α-dimethylbenzyl, NO_2, CHO, $CH_3CH(OH)$, $N(alkyl)_2$, acetyl, OCH_2COOH, and ethylene dioxy;

Ar_2 is either optionally substituted naphthyl, optionally substituted phenyl, or an optionally substituted heterocyclic aryl, wherein up to 5 substituents may be present and each substituent is independently selected from the group consisting of: alkyl, alkenyl, halogen, alkoxy, thioalkyl, methylene dioxy, haloalkyl, haloalkoxy, OH, CH_2OH, $CONH_2$, CN, OCH_2COOH, ethylene dioxy, and acetoxy;

R_2 and R_3 are each independently either hydrogen, alkyl, alkenyl or together cycloalkyl or cycloalkenyl;

R_7 is either hydrogen, alkyl or phenyl;

R_8 is either hydrogen, or alkyl;

R_9 is either hydrogen, alkyl or phenyl;

and pharmaceutically acceptable salts and complexes thereof;

wherein said compound is an ionomimetic modulating one or more inorganic ion receptor activities.

24. The compound of claim 23, wherein

Ar_1 is said optionally substituted heterocyclic aryl,

R_2 and R_3 are each independently hydrogen, alkyl, or together either cycloalkyl, provided that at least one of R_2 and R_3 is not hydrogen;

R_7 is hydrogen;

R_8 is hydrogen; and

R_9 is either hydrogen or lower alkyl;

wherein said compound is a calcimimetic modulating one or more calcium receptor activities.

25. The compound of claim 24, wherein R_2 is not hydrogen.

26. The compound of claim 25, wherein R_2 and R_3 are both methyl.

27. The compound of any of claims 23-25, wherein R_3 is hydrogen.

28. The compound of any of claims 23-27, wherein R_1 is alkyl.

29. The compound of claim 28, wherein said R_1 alkyl has more than one carbon atom.

30. The compound of any of claims 23-27, wherein R_1 is hydrogen.

31. The compound of any of claims 23-30, wherein Ar_2 is a substituted phenyl.

32. The compound of claim 31, wherein said Ar_2 substituted phenyl has one to four independently selected substituents, provided that at least one substituent is located in the *meta* position.

33. The compound of claim 31, wherein said Ar_2 substituted phenyl has 1 to 4 substituents each independently selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3.

34. The compound of claim 31, wherein said Ar_2 substituted phenyl has 1 to 4 substituents each independently selected from the group consisting of: isopropyl, CH_3O, CH_3S,

CF_3O, Br, I, Cl, F, CF_3, and CH_3, provided that at least one substituent is located in the *meta* position.

35. The compound of any of claims 23-30, wherein Ar_2 is an optionally substituted naphthyl.

36. The compound of claim 35, wherein Ar_2 is an unsubstituted naphthyl.

37. The compound of claim 35, wherein Ar_2 is a substituted naphthyl.

38. The compound of claim 37, wherein said Ar_2 substituted naphthyl has 1 to 4 independently selected substituents.

39. The compound of claim 38, wherein said Ar_2 substituted naphthyl has 1 to 4 independently selected substituents each selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3.

40. The compound of claim 30, wherein said Ar_2 substituted naphthyl has 1 substituent selected from the group consisting of: isopropyl, CH_3O, CH_3S, CF_3O, Br, I, Cl, F, CF_3, and CH_3.

41. A calcium receptor-active compound selected from the group consisting of: 25Z, 26A, 26B, 26C, 26D, 26E, 26F, 26G, 26H, 26I, 26J, 26K, 26L, 26M, 26N, 26O, 26P, 26Q, 26R, 26S, 26T, 26U, 26V, 26W, 26X, 26Y, 26Z, 27K, 27L, 27M, 27N, 27H, 28K, and pharmaceutically acceptable salts and complexes thereof.

42. The compound of claim 41, wherein said compound is selected from the group consisting of: 26A, 26D, 26F, and 26G.

43. A pharmaceutical composition comprising the compound of any of claims 1-42 and a pharmaceutical acceptable carrier.

44. A method for treating a patient in need of such treatment comprising the step of administering to said patient a therapeutically effective amount of the compound of any of claims 1-42.

45. The method of claim 44, wherein said disease is characterized by either, or both, of: (1) abnormal calcium homeostasis, and (2) an abnormal amount of an extracellular or intracellular messenger whose production can be affected by calcium receptor activity; and said compound is a calcimimetic.

46. The method of claim 44, wherein said disease is selected from the group consisting of: primary and secondary hyperparathyroidism, Paget's disease, hypercalcemia malignancy, osteoporosis, hypertension, and renal osteodystrophy.

47. The method of claim 46, wherein said disease is selected from the group consisting of primary and secondary hyperparathyroidism.

48. A method of decreasing serum PTH in a patient comprising the step of administering to said patient an effective amount of the compound of any of claims 1-42.

49. The method of claim 48, wherein serum PTH level is reduced to a degree sufficient to cause a decrease in plasma Ca^{2+}.

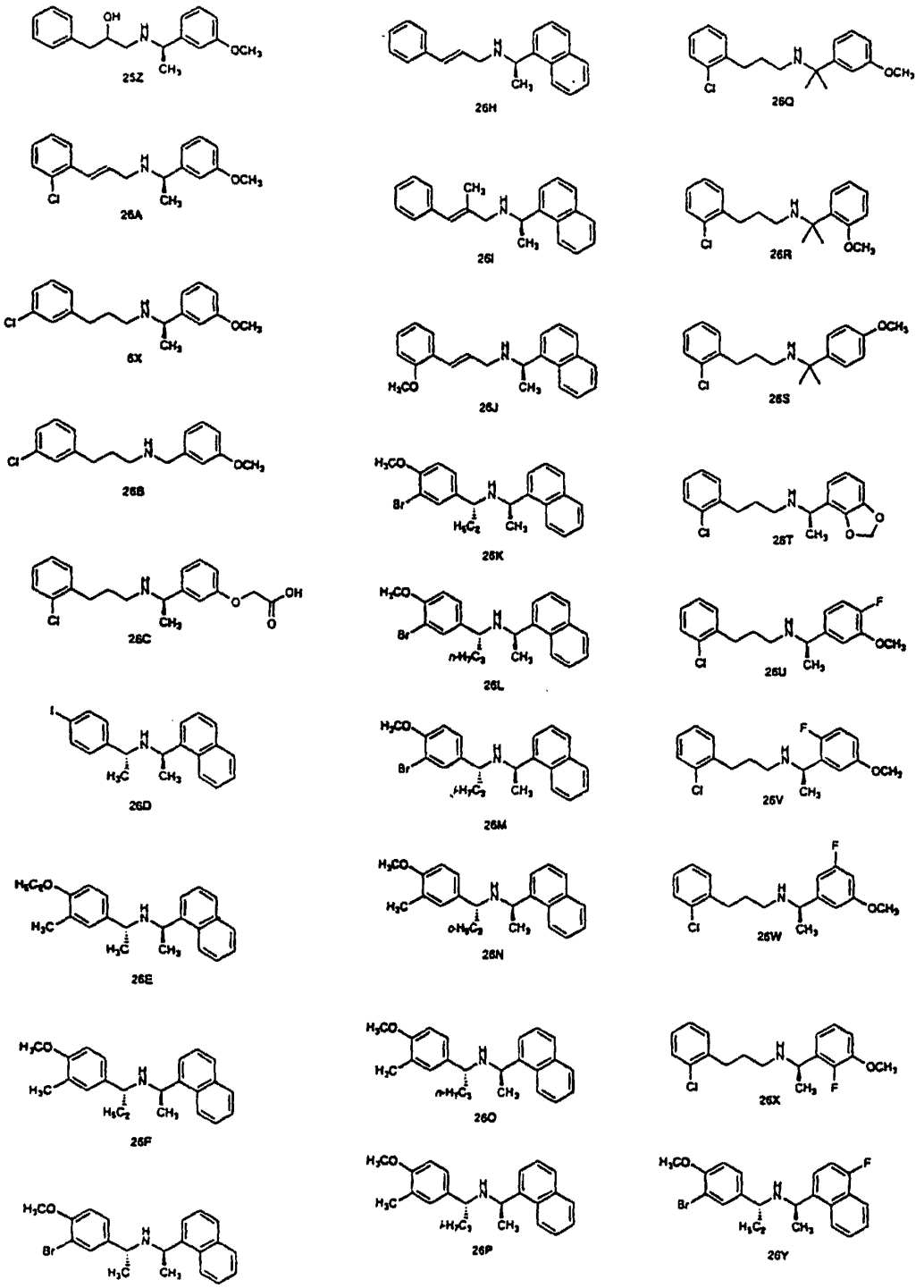
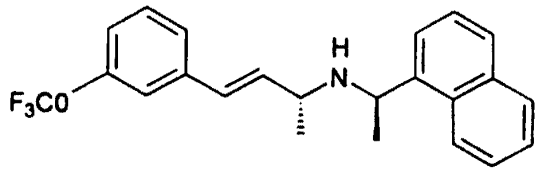


Fig. 1

SUBSTITUTE SHEET (RULE 26)



26Z

Fig. 2

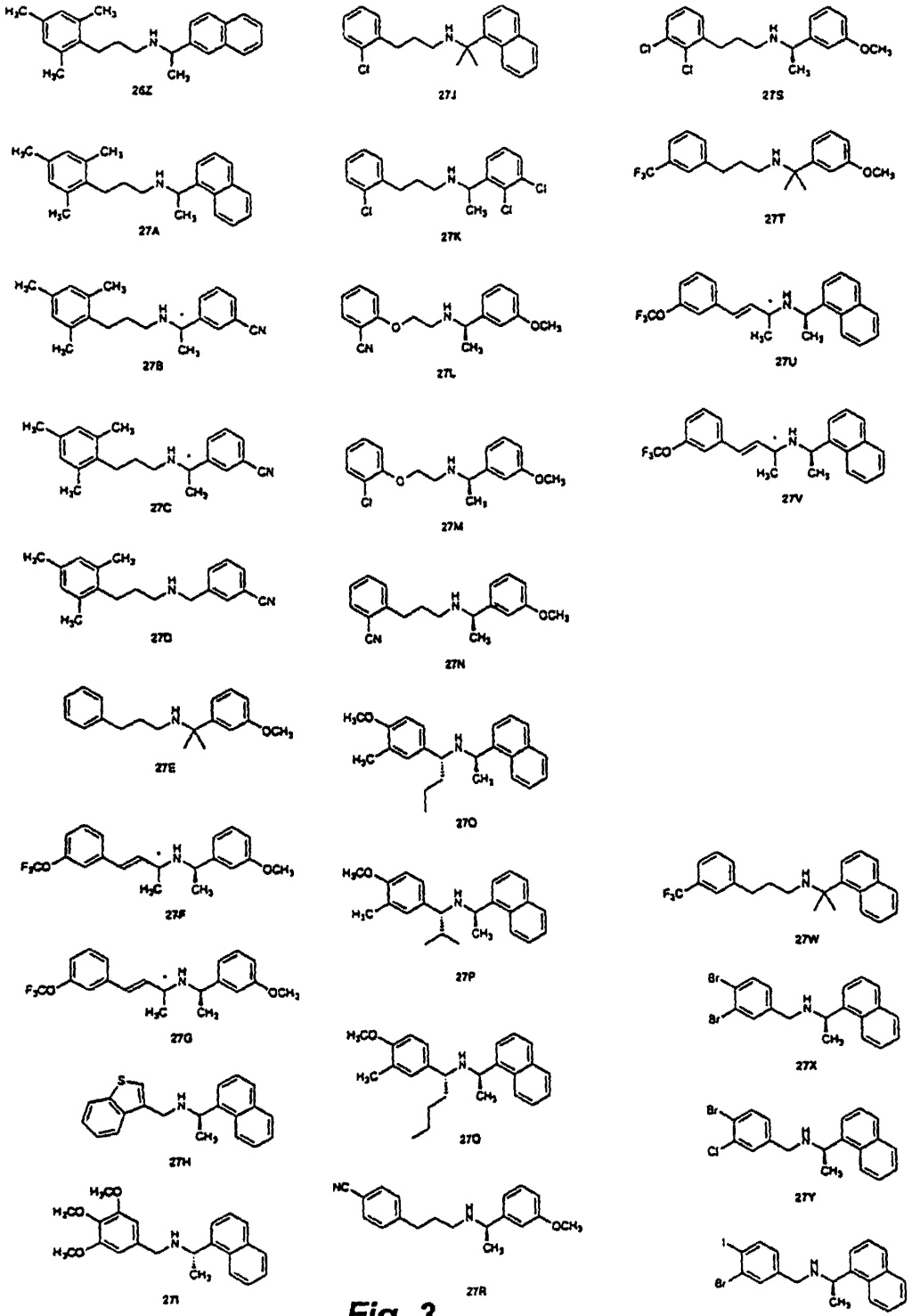


Fig. 3

SUBSTITUTE SHEET (RULE 26)

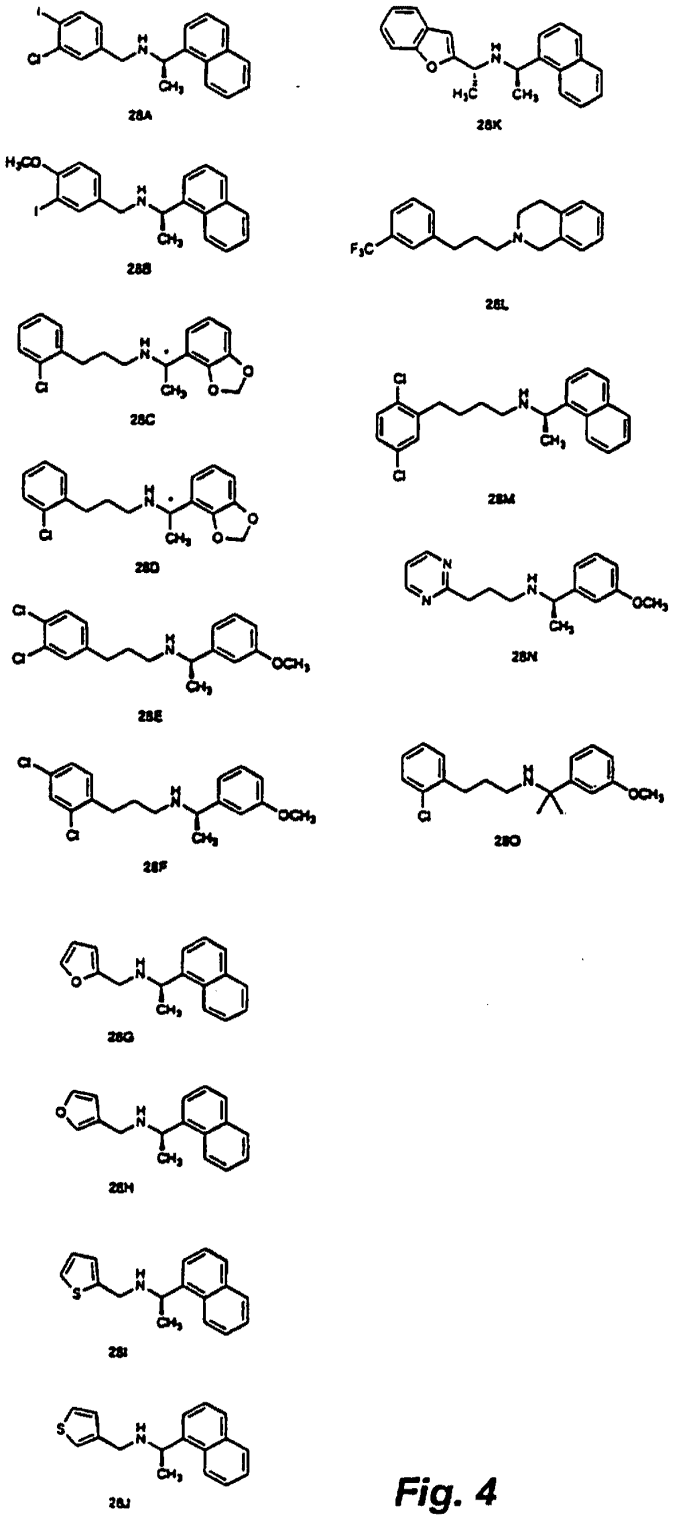


Fig. 4

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 97/07371

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C211/27 C07C211/28 C07C211/30 A61K31/135

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 12697 A (NPS PHARMACEUTICALS) 2 May 1996 see claims; figures	1,4,5, 7-23,25, 27,30, 43-49
X	WO 95 11221 A (NPS PHARMACEUTICALS) 27 April 1995 cited in the application see claims; figures	1,2,4,5, 7-23,25, 27,30, 43-49
X	WO 94 18959 A (NPS PHARMACEUTICALS) 1 September 1994 cited in the application see claims 1,25-35,99-102; figures 36b-d,36f,36j-t	1,2,4,5, 7-17,21, 22,43-49

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

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1997	21.08.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Zervas, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 97/07371

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 04373 A (NPS PHARMACEUTICALS) 4 March 1993 cited in the application see claims 1,25-35,99-102, figures 36b-d,36f,36j-t	1,2,4,5, 7-17,21, 22,43-49
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, no. 1, January 1986, WASHINGTON US, pages 112-125, XP002037080 ANTON STÜTZ ET AL.: "Synthesis and Structure-Activity Relationships of Naftifine-Related Allylamine Antimyotics" see page 117, table III, compound 34	23,27, 30,43
X	EP 0 092 787 A (SCHERING) 2 November 1983 see page 10, line 12 - page 11, line 23; claim 9	1,4,5,7, 8,21
X	DE 35 41 181 A (BASF) 27 May 1987 see claim 1; examples 94-100,104	1,4,7,8, 10-14,21
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002037081 see Beilstein Registry Number 7348908 & J. CHEM. RES. MINIPRINT, vol. 10, - 1981 pages 3529-3549,	1,21
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002037082 see Beilstein Registry Number 2756413 & ARZNEIM. FORSCH., vol. 17, 1967, pages 1145-1149,	1,7, 10-14,21
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002037083 see Beilstein Registry Number 6793469 & J. CHEM. SOC. CHEM. COMMUN., 1995, pages 1421-1422,	1,4,5,7, 10,16,22

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr. al Application No
PCT/US 97/07371

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002037084 see Beilstein Registry Number 5564574 & CHEM. PHARM. BULL., vol. 31, 1983, pages 3471-3485, ---	1,4,5,7, 10,16,22
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002037085 see Beilstein Registry Number 6148053 & ARCH. PHARM., vol. 326, 1993, pages 341-350, -----	1,4,5,7, 16,22

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/07371

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 44-49
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-40, 43-49
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see annex

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

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

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The definition of the substituents in the claims 1 to 40 and 43 to 49 is too general and encompasses too broad a range of possible combinations of different chemical groups, only partly supported by the examples given in the descriptive part of the application. Guided by the spirit and the descriptive part of the application the search has been based on the examples (cf Art. 6 PCT) and the claims 1 to 40 and 43 to 49 have been searched incompletely. Even this incomplete search revealed too many pertinent documents, which for economical reasons could not all be cited in the search report. All documents disclosing inorganic ion receptor-active compounds, which have been retrieved during the incomplete search are cited in the search report.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ..al Application No
PCT/US 97/07371

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 97/07371

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0224163 A	03-06-87
		JP 62181242 A	08-08-87
		US 4967003 A	30-10-90

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17 mai 2001 (17.05.2001)

PCT

(10) Numéro de publication internationale
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(21) Numéro de la demande internationale:
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(30) Données relatives à la priorité:
99/14050 9 novembre 1999 (09.11.1999) FR

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(75) Inventeurs/Déposants *(pour US seulement)*: RUAT, Martial [FR/FR]; 2, rue du Clos St Cyr, F-92340 Bourg-la-Reine (FR). POTIER, Pierre, Jean-Paul, Serge, Jacques [FR/FR]; 14, avenue de Breteuil, F-75007 Paris (FR). DODD, Robert [FR/FR]; 17, rue du Faubourg Montmartre, F-75009 Paris (FR). DAUBAN, Philippe, Marcel [FR/FR]; 71, rue Edouard Branly, F-91700 Sainte-Geneviève des Bois (FR). FAURE, Hélène, Véronique [FR/FR]; 84, allée des Fours Blancs, F-91190 Gif-sur-Yvette (FR).

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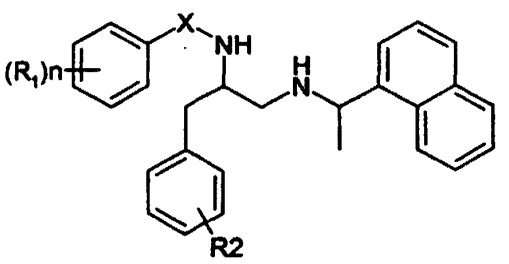
(81) États désignés *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) États désignés *(régional)*: brevet ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Suite sur la page suivante]

(54) Title: ARALKYL-1,2-DIAMINES HAVING CALCIMIMETIC ACTIVITY AND PREPARATION MODE

(54) Titre: ARALKYLE-1,2-DIAMINES POSSEDANT UNE ACTIVITE CALCIMIMETIQUE ET LEUR MODE DE PREPARATION



(I)

(57) Abstract: The invention concerns compounds of general formula (I) wherein: X represents a SO_2 or CH_2 group; R1 represents a hydrogen or halogen atom or an alkoxy, aryl aralkyl group or an alkyl group substituted or not with one or several halogen atoms, n is equal to 0, 1 or 2, and R2 represents a hydrogen or halogen atom or an alkyl or alkoxy group, and their salt with a pharmaceutically acceptable acid. The invention also concerns the method for preparing said compounds, pharmaceutical compositions containing them and their use as modulator of CaSR activity and as medicine particularly designed for treating diseases or physiological disorders involving modulation of CaSR activity.

(57) Abrégé: La présente invention concerne donc les composés de formule générale (I) dans laquelle: le groupe X représente un groupe SO_2 ou CH_2; le groupe R1 représente un atome d'hydrogène ou d'halogène ou un groupe alkoxy, aryle, aralkyle ou un groupe alkyle substitué ou non par un ou plusieurs atomes d'halogènes; n est égale à 0, 1 ou 2, et le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy, et leur sel avec un acide pharmaceutiquement acceptable. Elle concerne également leur préparation, les compositions pharmaceutiques les comprenant et leur utilisation comme modulateur de l'activité CaSR et comme médicament destiné de préférence au traitement des maladies ou des désordres physiologiques faisant intervenir la modulation de l'activité des CaSR.

WO 01/34562 A1

Publiée:
— *Avec rapport de recherche internationale.*

En ce qui concerne les codes à deux lettres et autres abréviations, se référer aux "Notes explicatives relatives aux codes et abréviations" figurant au début de chaque numéro ordinaire de la Gazette du PCT.

TITRE : **ARALKYLE-1,2-DIAMINES POSSEDANT UNE ACTIVITE CALCIMIMETIQUE ET LEUR MODE DE PREPARATION**

La présente invention décrit une nouvelle classe de composés, les aralkyl-1,2-diamines, leur préparation, les compositions pharmaceutiques les comprenant et leur utilisation comme modulateur de l'activité des récepteurs aux ions $(Ca^{2+})_e$ et $(Mg^{2+})_e$ ou CaSR pour Calcium Sensing Receptor et comme médicament destiné de préférence au traitement des maladies ou des désordres physiologiques faisant intervenir la modulation de l'activité des CaSR.

Ces composés présentent donc une activité calcimimétique, c'est à dire capable de produire ou d'induire des réponses biologiques observées par les variations de la concentration des ions calcium extracellulaires $(Ca^{2+})_e$ et des ions magnésium extracellulaires $(Mg^{2+})_e$.

Les ions $(Ca^{2+})_e$ et $(Mg^{2+})_e$ jouent un rôle majeur dans l'organisme car ils régulent l'homéostasie caicique dont dépendent les fonctions vitales de l'organisme. Ainsi, les hypercalcémies, c'est à dire des états ou les ions $(Ca^{2+})_e$ sont au-dessus du seuil moyen, ont une incidence majeure sur de nombreuses fonctions telles que les fonctions cardiaques, rénales ou intestinales. Elles affectent profondément le système nerveux central (voir revue Chattopadhyay et al, Endocr. Review, 1998).

Les CaSR sont des protéines sensibles aux ions $(Ca^{2+})_e$ et $(Mg^{2+})_e$ et sont présentes dans les glandes parathyroïdiennes, thyroïdiennes, le rein, l'intestin, les poumons, les cellules osseuses, le cerveau, la moelle épinière, l'hypophyse, l'estomac, les kératinocytes (Brown et al, Nature, 1993 ; Ruat et al, Proc. Natl. Acad. Sci., USA, 1995 ; voir revue Brown et al, Ann. Rev. Med., 1998). Ces protéines sont codées par un seul gène isolé dans différentes espèces animales. Elles appartiennent à la famille des récepteurs couplés aux protéines G à sept domaines transmembranaires, et présentent des homologies de structure avec les récepteurs métabotropiques du glutamate, des récepteurs $GABA_B$, des récepteurs hypothétiques aux phéromones et du goût. Des mutations activatrices ou inhibitrices du gène chez l'homme sont responsables de maladies génétiques extrêmement graves qui provoquent des hypocalcémies ou des hypercalcémies (Pollack et al, Cell, 1993 ; Pollack et al, Nature Genetic, 1994 ; voir revue Brown et al, Ann. Rev.

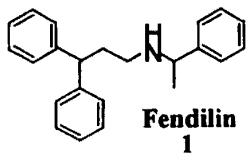
Med., 1998). Les fonctions liées à l'expression de ces protéines dans les tissus ne sont pas encore toutes connues et font l'objet d'une très grande activité de recherche, particulièrement en ce qui concerne les CaSR présents dans les glandes parathyroïdiennes, thyroïdiennes, le rein, l'intestin, la moelle épinière, le cerveau et les cellules osseuses.

Dans la glande parathyroïdienne, les CaSR modulent la sécrétion de l'hormone parathyroïdienne (PTH) qui est le principal régulateur de l'homéostasie calcique: l'augmentation des ions $(Ca^{2+})_e$ dans le sérum va activer les CaSR présents sur les cellules de la glande parathyroïdienne et diminuer la sécrétion de l'hormone PTH.

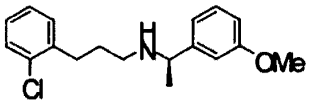
L'ADN complémentaire codant pour le CaSR de rat a été isolé à partir d'une banque ADNc de striatum de rat (Ruat et al, Proc. Natl. Acad. Sci., 1995). Ce récepteur est identique au niveau de sa séquence en acides aminés à celui exprimé dans les autres tissus. Des cellules ovariennes de hamster chinois (CHO) transfectées exprimant le CaSR de rat (CHO(CaSR)) ont été caractérisées et les signaux chimiques (seconds messagers) induits par l'activation de ce récepteur ont été analysés. Ainsi, un test biochimique permettant de mesurer l'accumulation d'inositols phosphates tritiés [^{3}H]IP en réponse à l'activation du récepteur a été mis au point (Ruat et al, J. Biol. Chem., 1996 ; Ferry et al, Biochem. Biophys. Res. Commun., 1997).

Il a été montré que les ions Ca^{2+}, Mg^{2+}, mais aussi Ba^{2+} dans des gammes de concentrations millimolaires stimulent les CaSR. L'activation des CaSR pourrait être induite dans le cerveau par les peptides β-amyloides, qui sont impliqués dans des maladies neurodégénératives telles que la maladie d'Alzheimer (Ye et al, J. Neurosci. Res., 1997).

Le composé NPS R-568 (1), ligand allostérique du CaSR, appartient à la première et, jusqu'à présent, seule famille de molécules organiques de petite taille ($M < 600$), interagissant avec ce récepteur. Cette arylalkylamine a été développée à partir de la structure de la Fendiline (2), un puissant activateur du CaSR de la glande parathyroïdienne.

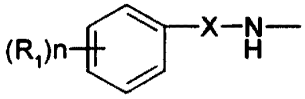


Fendilin
1



NPS R-
2

Les composés PHD selon la présente invention, ont une structure différente de ceux de cette famille par la présence d'un groupement



Ce groupement représente un site d'interaction de cette molécule avec les récepteurs CaSR.

L'hyperparathyroïdie secondaire est observée lors d'insuffisance rénale chronique et se caractérise par une hyperplasie des glandes parathyroïdiennes et une augmentation de la PTH circulante. L'insuffisance rénale est aussi accompagnée d'ostéodystrophie rénale qui se caractérise par des désordres osseux avec un fort ou un faible renouvellement de la masse osseuse (ostéitis fibrosa, osteomalacia). L'agent NPS-R-568 réduit ou élimine l'ostéitis fibrosa chez le rat (Wada et al, Kidney International, 1998) et réduit les concentrations de PTH chez des patients (hommes) souffrant d'insuffisance rénale chronique (Antansen et al, Kidney International, 1998). Ce composé a été utilisé par voie orale avec succès pour abaisser les concentrations de PTH et des ions Ca^{2+} libres sériques chez la femme ménopausée souffrant d'hyperparathyroïdie primaire (Silverberg et al, New Engl. J. Med., 1997). Dans une autre étude, le composé NPS-R-568 a permis de réduire entre 20-50 % la prolifération cellulaire observée dans la glande parathyroïdienne chez un modèle de rat reproduisant l'insuffisance rénale chronique (Wada et al, J. Clin. Invest., 1997). Ces études démontrent qu'un composé calcimimétique, actif vis-à-vis du récepteur au calcium présent sur la glande parathyroïde, peut-être considéré comme un outil thérapeutique intéressant pour traiter certaines formes d'hyperparathyroïdies primaires et secondaires.

Durant des essais cliniques, (Phase I - II) la société NPS Pharmaceutical a observé une bio-disponibilité faible du composé NPS-R-568 ainsi que des effets cliniques variables suivant les individus qui pourraient provenir de polymorphisme

du gène codant pour le CaSR chez l'homme (Nemeth et al, Trends Endoc. Metab, 1999). Dans cette invention, les molécules synthétisées présentent des avantages par rapport au composé NPS-R-568 car leur structure fait apparaître plusieurs sites d'interaction avec le CaSR.

De plus, lors d'essais expérimentaux chez le rat, le composé NPS R-467, un composé de structure voisine du NPS R-568, s'est avéré plus sélectif vis à vis des récepteurs de la parathyroïde comparativement à ceux de la glande thyroïde. Cette sélectivité peut s'expliquer par des différences liées aux tissus ce qui suggère que des molécules calcimimétiques spécifiques d'un tissu peuvent être synthétisées et avoir des importances cliniques considérables. Du fait de la présence de nouveaux groupements capables d'interagir avec le CaSR ou avec son système de transduction, les molécules de la présente invention se révélent intéressantes en clinique.

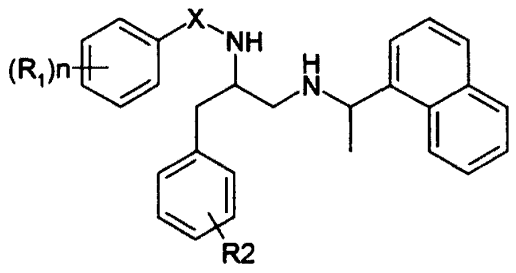
L'ostéoporose est une maladie multifactorielle qui dépend notamment de l'âge et du sexe. Si les femmes ménopausées sont très fortement touchées, l'ostéoporose s'avère de plus en plus un problème chez l'homme âgé, et il n'existe pas pour l'instant de traitements vraiment satisfaisants. Son coût social pourrait s'alourdir encore dans les prochaines années, particulièrement dans notre société européenne ou la durée de vie s'allonge. L'ostéoporose est actuellement traitée par les œstrogènes, la calcitonine ou les biphosphonates qui préviennent la résorption osseuse sans stimuler une nouvelle croissance osseuse. Des données plus récentes démontrent que des augmentations intermittentes de la PTH ou de ses dérivés, sont efficaces dans le traitement de l'ostéoporose et permettent de remodeler l'os en stimulant la formation osseuse (Whitfield et al, 1999). Cette nouvelle voie thérapeutique du traitement de l'ostéoporose apparaît très intéressante bien que des problèmes majeurs soient liés à l'utilisation de l'hormone PTH tels que la voie d'injection, mais aussi l'apparition de tumeurs observées récemment durant des essais cliniques chez l'homme. La sécrétion intermittente de PTH endogène peut être obtenue par le blocage du récepteur au calcium. Le blocage de la sécrétion de PTH par les agonistes du CaSR peut être suivie par une augmentation rapide de la PTH (effet rebond), qui est alors bénéfique dans le traitement de l'ostéoporose.

Ainsi, les molécules décrites dans l'invention s'avèrent utiles pour moduler l'activité du CaSR dans la glande parathyroïde, la thyroïde, les cellules osseuses,

l'estomac, le poumon, le rein, l'hypophyse, le cerveau. Elles s'avèrent aussi utilisables pour modifier l'activité de CaSR présents dans l'hypothalamus, les aires olfactives, l'hippocampe, pour traiter des maladies démyélinisantes associées à l'expression des CaSR dans les oligodendrocytes.

La présente invention décrit donc de nouvelles molécules destinées à traiter les désordres biologiques liés à des perturbations de l'activité des CaSR telles que les hyperparathyroïdies primaires et secondaires, l'ostéoporose, les maladies cardio-vasculaires, gastro-intestinales, endocrines, neurodégénératives, ou encore certains cancers où les ions $(Ca^{2+})_e$ sont anormalement élevés. L'absence totale de molécules calcimimétiques en clinique, et les problèmes rencontrés en phase I-II pour les calcimimétiques de première génération, soulignent l'intérêt des molécules décrites dans l'invention, celles-ci ayant de plus un site d'interaction supplémentaire avec les récepteurs CaSR.

La présente invention concerne donc les composés de formule générale I :



I

dans laquelle :

le groupe X représente un groupe SO_2 ou CH_2,

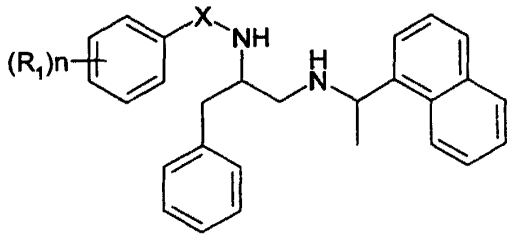
le groupe R1 représente un atome d'hydrogène ou d'halogène ou un groupe alkoxy, aryle, aralkyle ou un groupe alkyle substitué ou non par un ou plusieurs atomes d'halogènes,

n est égale à 0, 1 ou 2,

et le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy,

et leur sel avec un acide pharmaceutiquement acceptable.

De préférence, les composés selon l'invention sont représentés par la formule générale (II) :



II

dans laquelle :

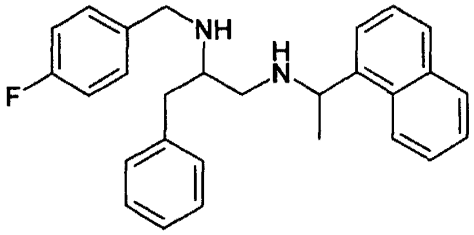
le groupe X représente un groupe SO_2 ou CH_2,

le groupe R1 représente un atome d'hydrogène ou d'halogène ou un groupe alkoxy, aryle, aralkyle ou un groupe alkyle substitué ou non par un ou plusieurs atomes d'halogènes,

et n est égale à 0, 1 ou 2.

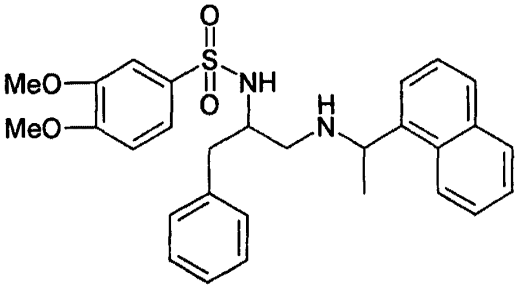
De façon encore plus préférentiel, le groupe R1 est un noyau benzo ou alkylbenzo fusionné

Des exemples de composés préférés selon l'invention sont ceux ayant pour formule (III) :



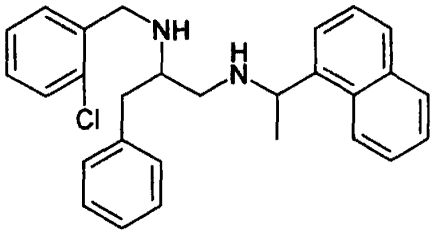
III

ou (IV) :



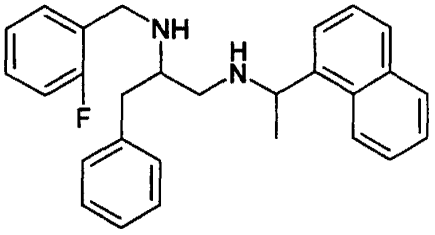
IV

ou (V) :



V

ou (VI) :



VI

Les acides pharmaceutiquement acceptables sont des acides non toxiques, y compris les acides organiques et inorganiques. De tels acides incluent l'acide acétique, benzènesulfonique, benzoïque, citrique, éthanesulfonique, fumarique, gluconique, glutamique, bromhydrique, chlorhydrique, lactique, maléique, malique, mandélique, méthanesulfonique, mucique, nitrique, pamoique, pantothénique, phosphorique, succinique, sulfurique, tartarique et paratoluènesulfonique. L'acide chlorhydrique est particulièrement préféré.

Par le terme de groupe alkyle, on entend les groupes alkyles de 1 à 4 atomes de carbones, linéaires ou ramifiés, substitués ou non substitués. Un exemple préféré de groupes alkyles est le groupes CH_3. Un exemple préféré de groupe alkyle substitué par des atomes d'halogène est le groupe CF_3.

Par le terme de groupe alkoxy, on entend les groupes alkoxys de 1 à 4 atomes de carbones, linéaires ou ramifiés, substitués ou non substitués. Un exemple préférés de groupes alcényles est OCH_3.

Par le terme de groupes aryles on entend des cycles aromatiques ayant de 4 à 8 atomes de carbones, substitués ou non substitués, ayant un seul ou plusieurs noyau aromatiques. Les cycles aromatiques peuvent être accolés ou fusionnés entre

eux ou fusionné au cycle aromatique présent dans la molécule de départ. Un exemple de groupe aryle préféré est un groupe benzo fusionné.

Par le terme de groupes aralkyles on entend des groupes aryles, définis comme ci-dessus, liés au groupe phényle par l'intermédiaire d'un groupe alkyle défini comme précédemment.

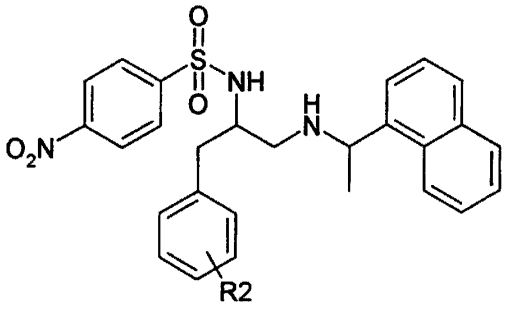
Des exemples préférés d'atome d'halogène sont Cl et F.

Les composés selon l'invention possèdent tous un centre d'asymétrie et peuvent donc exister sous forme d'isomères optiques. La présente invention comprend aussi bien ces isomères soit séparément soit en tant que mélange.

La présente invention concerne également le mode de préparation de ces composés qui peut être le suivant :

- Dans le cas où X représente le groupe SO_2, le procédé de préparation comporte les étapes suivantes :

a) le composé de formule (VII) :



VII

dans laquelle :

le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy

subit une réaction de déprotection

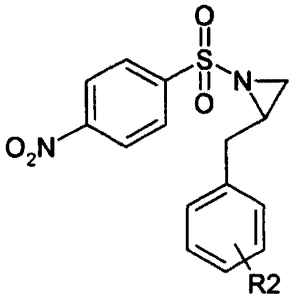
b) un groupement arylsulfonyle est introduit sélectivement sur une de ses fonctions amines du composé obtenu.

- Dans le cas où X représente le groupe CH2 le procédé de préparation comporte les étapes suivantes :

a) un groupement arylbenzyle est introduit sélectivement sur une des fonctions amines du composé de formule (VII)

b) le composé obtenu subit une réaction de déprotection.

Le composé de formule (VII) est obtenu par ouverture nucléophile par la 1-(1-naphtyl)éthylamine de la 2-benzyl-1-(*p*-nitrobenzènesulfonyl)aziridine de formule générale (VIII) :

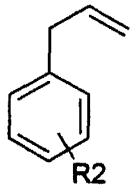


VIII

dans laquelle :

le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy.

Le composé de formule (VIII) est obtenu par réaction entre une oléfine de formule générale (IX) :



IX

dans laquelle :

le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy

et PhI=NSO_2Ph-*p*-NO_2 en présence de $Cu^{I\ ou\ II}$ et de CH_3CN.

La présente invention concerne également les compositions pharmaceutiques comprenant à titre de principe actif un des composés définis ci-dessus et un excipient approprié. Ces compositions peuvent être formulées pour l'administration aux mammifères, y compris l'homme. La posologie varie selon le traitement et selon l'affection en cause. Ces compositions sont réalisées de façon à pouvoir être administrées par la voie digestive ou parentérale.

Dans les compositions pharmaceutiques de la présente invention pour l'administration orale, sublinguale, sous-cutanée, intramusculaire, intraveineuse, transdermique, locale ou rectale, l'ingrédient actif peut être administré sous formes unitaires d'administration, en mélange avec des supports pharmaceutiques classiques, aux animaux ou aux êtres humains. Les formes unitaires d'administration appropriés comprennent les formes par voie orale telles que les comprimés, les gélules, les poudres, les granules et les solutions ou suspensions orales, les formes d'administration sublinguale et buccale, les formes d'administration sous-cutanée, intramusculaire, intraveineuse, intranasale ou intraoculaire et les formes d'administration rectale.

Lorsque l'on prépare une composition solide sous forme de comprimés, on mélange l'ingrédient actif principal avec un véhicule pharmaceutique tel que la gélatine, l'amidon, le lactose, le stéarate de magnésium, le talc, la gomme arabique ou analogues. On peut enrober les comprimés de saccharose ou d'autres matières appropriées ou encore on peut les traiter de telle sorte qu'ils aient une activité prolongée ou retardée et qu'ils libèrent d'une façon continue une quantité prédéterminée de principe actif.

On obtient une préparation en gélules en mélangeant l'ingrédient actif avec un diluant et en versant le mélange obtenu dans des gélules molles ou dures.

Une préparation sous forme de sirop ou d'élixir peut contenir l'ingrédient actif conjointement avec un édulcorant, un antiseptique, ainsi qu'un agent donnant du goût et un colorant approprié.

Les poudres ou les granules dispersibles dans l'eau peuvent contenir l'ingrédient actif en mélange avec des agents de dispersion ou des agents mouillants, ou des agents de mise en suspension, de même qu'avec des correcteurs du goût ou des édulcorants.

Pour une administration rectale, on recourt à des suppositoires qui sont préparés avec des liants fondant à la température rectale, par exemple du beurre de cacao ou des polyéthylèneglycols.

Pour une administration parentérale, intranasale ou intraoculaire, on utilise des suspensions aqueuses, des solutions salines isotoniques ou des solutions stériles et injectables qui contiennent des agents de dispersion et/ou des agents mouillants pharmacologiquement compatibles.

Le principe actif peut être formulé également sous forme de microcapsules, éventuellement avec un ou plusieurs supports additifs.

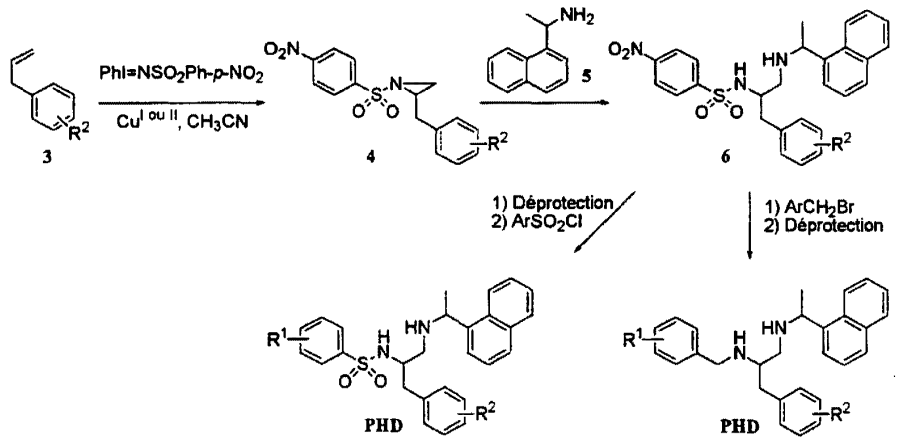
La présente invention concerne également l'utilisation des ces composés et des compositions pharmaceutiques les comprenant comme modulateur de l'activité du CaSR

Le CaSR peut se trouver dans la glande parathyroïde, la thyroïde, les cellules osseuses, l'estomac, le poumon, le rein, l'hypophyse, le cerveau, l'hypothalamus, les aires olfactives ou l'hippocampe.

Les composés selon la présente invention sont de préférence plus sélectifs dans leur utilisation vis à vis des récepteurs de la parathyroïde comparativement à ceux de la glande thyroïde.

Les composés selon l'invention et les compositions pharmaceutiques les comprenant peuvent être utilisés comme médicament, en particulier pour le traitement des maladies ou des désordres physiologiques liés à des perturbations de l'activité des CaSR. De façon encore plus particulière, ces maladies ou désordres physiologiques sont du type hyperparathyroïdies primaires ou secondaires, ostéoporose, maladies cardio-vasculaires, gastro-intestinales, endocrines, neurodégénératives ou certains cancers où les ions $(Ca^{2+})_e$ sont anormalement élevés. L'hyperparathyroïdie secondaire est plus particulièrement observée lors d'insuffisance rénale chronique.

La préparation des composés selon l'invention, décrite dans le schéma ci-dessous, implique l'ouverture nucléophile par la 1-(1-naphtyl)éthylamine (5) de la 2-benzyl-1-(*p*-nitrobenzènesulfonyl)aziridine (4), synthétisée en une étape à partir de l'oléfine 3. Selon l'ordre de la séquence de réactions de déprotection et protection effectuée sur le dérivé 6, il est alors possible d'introduire sélectivement un groupement arylsulfonyle ou benzyle sur une des fonctions amines. Un des intérêts de cette chimie originale est de pouvoir incorporer facilement un grand nombre de substituants variés R1 et R2.



Les exemples de synthèse suivants, donnés à titre non limitatif, illustrent l'invention.

Synthèse de la 2-Benzyl-1-(*p*-nitrobenzènesulfonyl)aziridine 4.

A une solution de trifluorométhanesulfonate de cuivre (I) (500 mg ; 0,9 mmole) dans 20 ml d'acétonitrile distillé, en présence de tamis moléculaire activé, sont successivement ajoutés, à 0°C sous argon, l'allylbenzène (1,60 ml ; 12 mmoles) et, par portions de 1 g sur une période de 36 heures, PhI=NSO_2Ph-*p*-NO_2 (4,85 g ; 12 mmoles). Le mélange hétérogène, de couleur marron puis verte, est agité à 0°C pendant 72 heures avant d'être filtré sur silice (Eluant : acétate d'éthyle) pour enlever le tamis moléculaire et les sels de cuivre. Après évaporation des solvants, le résidu huileux jaune est purifié par chromatographie sur silice (Eluant : heptane / acétate d'éthyle : 7 / 2) pour donner 1,76 g (5,53 mmoles ; 46%) d'un solide légèrement coloré.

Point de fusion : 107 °C (litt : 107-108 °C).

Synthèse du N^1-[1-(1-naphtyl)éthyl]-N^2-(4-nitrobenzènesulfonyl)-3-phényl-propane-1,2-diamine 6.

A une solution de l'aziridine 4 (956 mg ; 3,0 mmoles) dans 7 ml de THF sont successivement additionnées la triéthylamine (0,020 ml ; 0,15 mmole) et la 1-(1-naphtyl)éthylamine 5 (0,970 ml ; 6,00 mmoles). Après 2 jours d'agitation à température ambiante, le milieu est concentré avant d'être purifié sur colonne de

silice (Eluant : heptane / acétate d'éthyle : 2 / 1). 1,38 g (2,82 mmoles ; 94%) du composé 6 est isolé sous la forme d'une mousse jaune.

Point de fusion : 125-126 °C

Analyse élémentaire : $C_{27}H_{27}N_3O_4S$. 1/3 H_2O : Calculé : C, 65,44 ; H, 5,63 ; N, 8,48 ; S, 6,47. Trouvé : C, 65,27 ; H, 5,28 ; N, 8,36 ; S, 6,86.

Synthèse du N^2-(3,4-diméthoxybenzènesulfonyl)-N^1-[1-(1-naphtyl)éthyl]-3-phénylpropane-1,2-diamine PHD 321.

Le sulfonamide 6 (435 mg ; 0,888 mmole) est chauffé, à 50°C sous argon, dans une solution de thiophénol (0,270 ml ; 2,63 mmoles) et de carbonate de potassium (490 mg ; 3,54 mmoles) dans 10 ml d'un mélange 49/1 d'acétonitrile/DMSO. Après 6 heures de réaction, le milieu est concentré avant d'être purifié sur colonne de silice (Eluant : acétate d'éthyle / méthanol : 7 / 3) pour donner 250 mg (0,821 mmole ; 92%) de produit de déprotection.

94 mg (0,308 mmole) de ce composé en solution dans 3 ml de dichlorométhane sont mis en réaction en présence de 2 équivalents de triéthylamine (0,087 ml ; 0,619 mmole) et de 1,1 équivalent de chlorure de 3,4-diméthoxybenzènesulfonyle (80 mg ; 0,34 mmole). Après 24 heures d'agitation à température ambiante, le mélange est purifié sur colonne de silice (Eluant : heptane / acétate d'éthyle : 40 /60) pour donner 140 mg (0,277 mmole ; 90%) de PHD 321 sous la forme d'une huile incolore. Celle-ci, traitée par une solution d'acide chlorhydrique gazeux dans le dichlorométhane, est transformée en solide blanc correspondant au chlorhydrate du produit attendu.

Point de fusion : 186 °C

Spectrométrie de masse (IC) : m/z : 505 $[M+H]^+$

Synthèse du N^2-(2-Chlorobenzyl)-N^1-[1-(1-naphtyl)éthyl]-3-phénylpropane-1,2-diamine PHD 307.

Le sulfonamide 6 (88 mg ; 0,180 mmole) en solution dans 1,5 ml de DMF est traité à 0°C sous argon par 2 équivalents de K_2CO_3 (50 mg ; 0,361 mmole) et 1,1 équivalent de bromure de 2-chlorobenzyle (0,026 ml ; 0,200 mmole). Après 6 heures de réaction de 0°C à température ambiante, le milieu est filtré sur colonne de silice (Eluant : heptane / acétate d'éthyle : 6 / 1) pour conduire à 81 mg (0,132 mmole ; 73%) d'un solide blanc. Ce dernier est chauffé à 50°C sous argon dans un mélange de thiophénol (3 eq.) et de K_2CO_3 (4 eq.) en solution dans 1,5 ml

d'acétonitrile/DMSO : 49/1. Après 20 heures de réaction, la chromatographie sur colonne de silice (Eluant : heptane / acétate d'éthyle : 1 / 3) permet d'isoler 45 mg (0,105 mmole ; 80%) d'une huile incolore. Par traitement dans une solution d'HCl_{gaz} dans CH_2Cl_2, le chlorhydrate de PHD 307 est isolé sous la forme d'une poudre blanche.

Point de fusion : 129 °C

Spectrométrie de masse (FAB) : m/z : 429 $[M+H]^+$

Activité sur des cellules transfectées exprimant le récepteur sensible aux ions $(Ca^{2+})e$

L'activité calcimimétique des composés a été estimée en mesurant l'accumulation d'inositols phosphates tritiés induite par 10 µM de chacun des composés en présence de 2 mM de Ca^{2+} dans les cellules CHO(CaSR) (Ferry et al, Biochem Biophys Res Commun, 1997) .

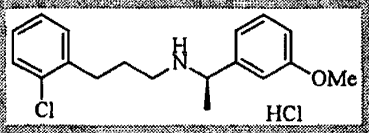
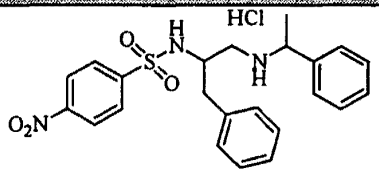
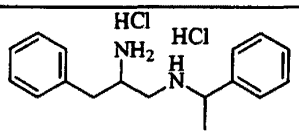
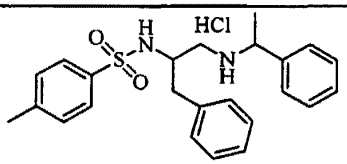
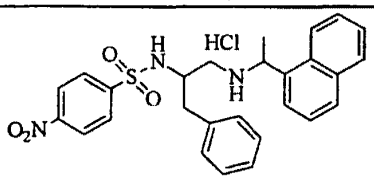
Cette activation a été comparée à celle induite par le composé NPS-R- 568, un calcimimétique de référence et utilisé à une concentration de 10 µM (Tableau 1) (Ferry et al, Biochem Biophys Res Commun, 1997 ; Nemeth et al, Proc Natl Acad Sci USA, 1997).

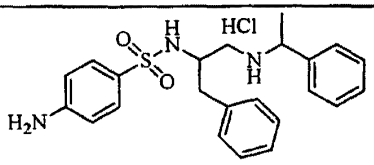
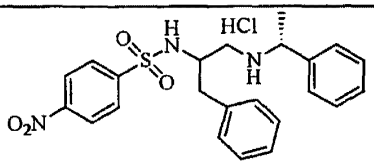
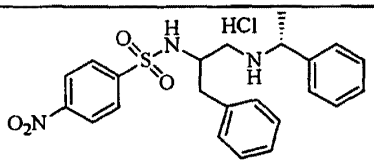
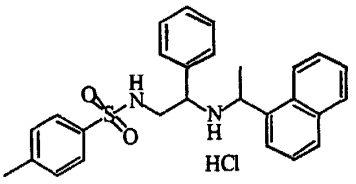
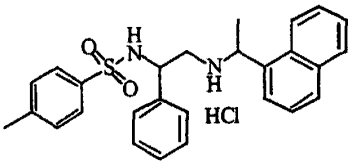
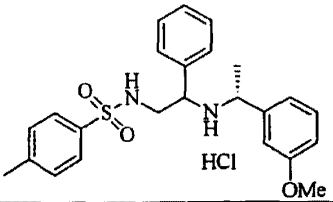
Les composés PHD 307, 320, 321 et 323, utilisés à une concentration de 10 µM présentent une activité allant de 90 à 100 % de celle obtenue par 10 mM de Ca^{2+}, alors que le NPS-R-568 présente une activité de 100 % à la même concentration. Dans cette série chimique certains composés tels PHD 90, 128, 129, 125, sont dépourvus d'activité calcimimétique à cette concentration (Tableau 1).

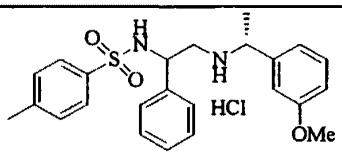
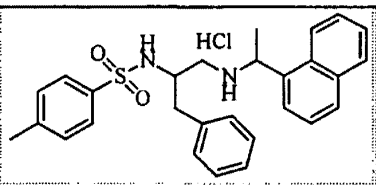
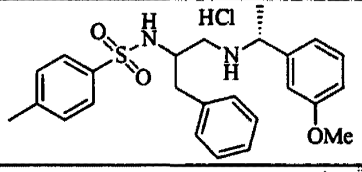
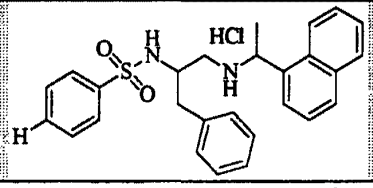
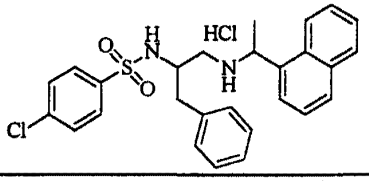
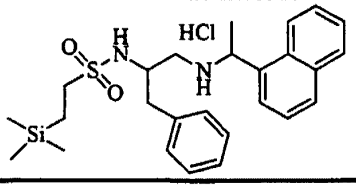
La comparaison de la structure des composés PHD 181 et PHD 182 d'une part et PHD 206 et PHD 217 d'autre part, indique que le groupement naphtyle conduit à une activité supérieure par rapport au groupement 3-méthoxyphényle.

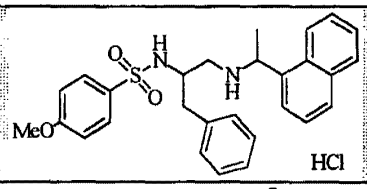
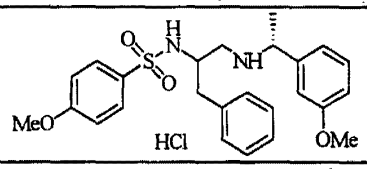
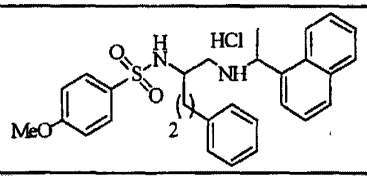
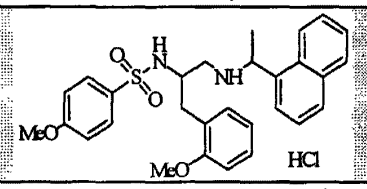
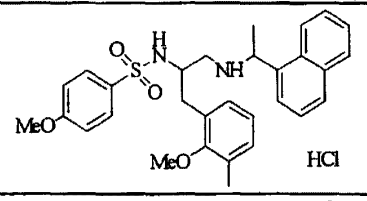
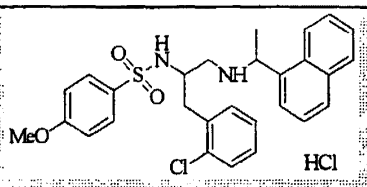
Dans le tableau 1, l'activité calcimimétique des composés PHD est comparée à celle d'un composé de référence, le NPS-R-568 utilisé à la même concentration et dans les mêmes conditions expérimentales. Cette activité est exprimée en pourcentage de l'activité de 10 mM de Ca^{2+}. Les moyennes ± erreurs standards de 2 à 5 manipulations indépendantes sont indiquées. Les expériences ont été réalisées en présence de 2 mM de Ca^{2+}.

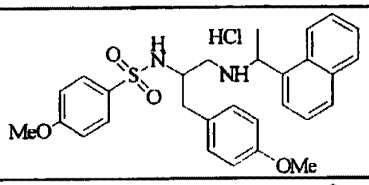
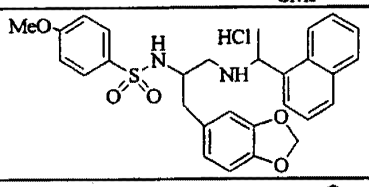
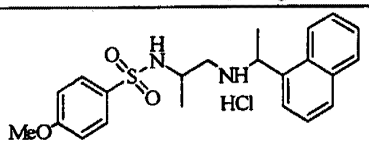
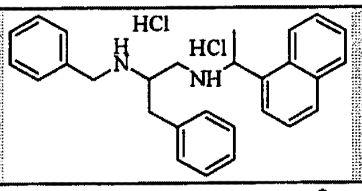
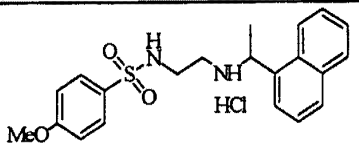
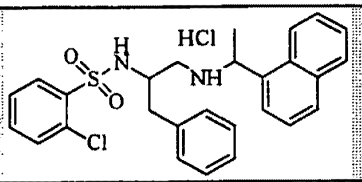
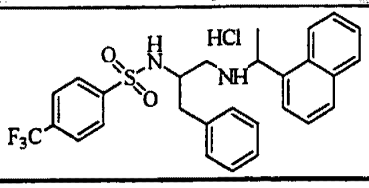
Tableau 1 : accumulation d'inositols phosphates tritiés dans les cellules CHO(CaSR) induite par les composés PHD et le composé calcimimétique NPS R-568

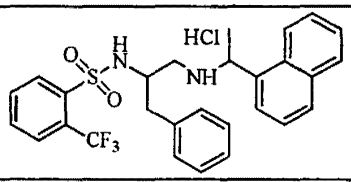
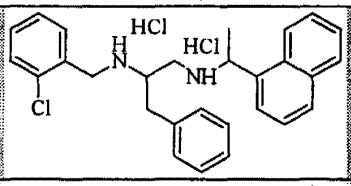
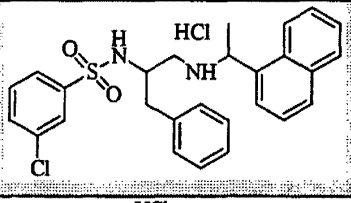
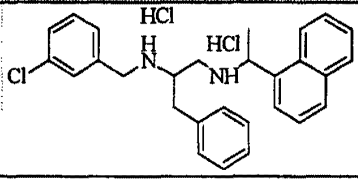
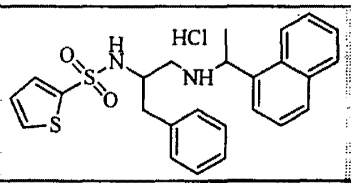
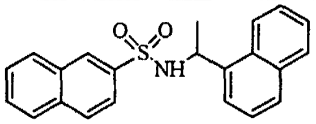
Composé - (10 µM)	Formule brute - Masse molaire (point de fusion)	Structure	Accumulation d'(^{3}H)-IP % de la réponse 10mM Ca^{2+} ± E.S.
NPS R-568	$C_{18}H_{22}ClNO.HCl$ 340,29		106 ± 15
PHD 87	$C_{23}H_{25}N_3O_4S.HCl$ 476,00		8 ± 4
PHD 90	$C_{17}H_{22}N_2.2HCl$ 327,30		3 ± 2
PHD 121	$C_{24}H_{28}N_2O_2S.HCl$ 445,01		23 ± 15
PHD 124	$C_{27}H_{27}N_3O_4S.HCl$ 526,05		27 ± 11

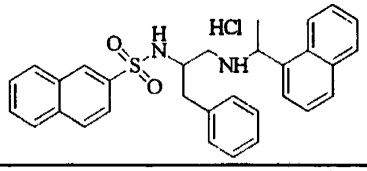
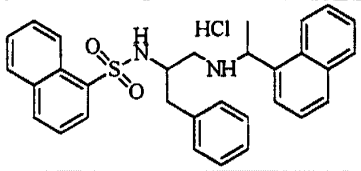
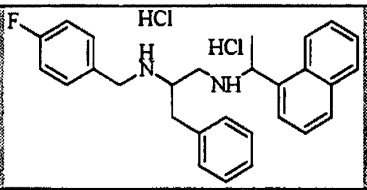
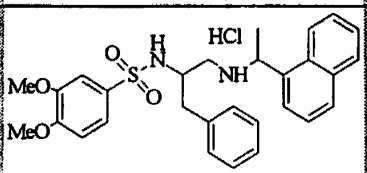
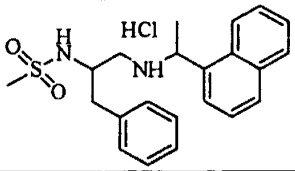
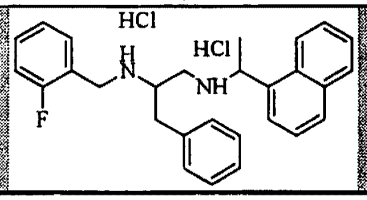
Composé - (10 µM)	Formule brute - Masse molaire (point de fusion)	Structure	Accumulation d'(^{3}H)-IP % de la réponse 10mM Ca^{2+} ± E.S.
PHD 125	**$C_{23}H_{27}N_3O_2S.HCl$** **446,00**		2 ± 4
PHD 127 A	**(*RS,R*) $C_{23}H_{25}N_3O_4S.HCl$** **476,00**		12 ± 5
PHD 127 B	**(*SR,R*) $C_{23}H_{25}N_3O_4S.HCl$** **476,00**		13 ± 3
PHD 176 A	**$C_{27}H_{28}N_2O_2S.HCl$** **481,05**		6 ± 1
PHD 176 B	**$C_{27}H_{28}N_2O_2S.HCl$** **481,05**		31 ± 3
PHD 178 A	**$C_{24}H_{28}N_2O_3S.HCl$** **460,05**		6 ± 6

Composé - (10 µM)	Formule brute - Masse molaire (point de fusion)	Structure	Accumulation d'(^{3}H)-IP % de la réponse 10mM Ca^{2+} ± ES
PHD 178 B	**$C_{24}H_{28}N_2O_3S.HCl$** **460,05**		22 ± 10
PHD 181	**$C_{28}H_{30}N_2O_2S.HCl$** **495,09 (188 °C)**		68 ± 9
PHD 182	**$C_{25}H_{30}N_2O_3S.HCl$** **475,05**		36 ± 12
PHD 202	**$C_{27}H_{28}N_2O_2S.HCl$** **481,06 (176 °C)**		78 ± 10
PHD 203	**$C_{27}H_{27}ClN_2O_2S.$ HCl** **515,50**		38 ± 20
PHD 204	**$C_{26}H_{36}N_2O_2SSi.$ HCl** **505,19**		34 ± 1

Composé - (10 µM)	Formule brute - Masse molaire (point de fusion)	Structure	Accumulation d'(^{3}H)-IP % de la réponse 10mM Ca^{2+} ± ES
PHD 206	**$C_{28}H_{30}N_2O_3S.HCl$** **511,08** **(118 °C)**		**80 ± 12**
PHD 217	**$C_{25}H_{30}N_2O_4S.HCl$** **491,05**		34 ± 5
PHD 218	**$C_{29}H_{32}N_2O_3S.HCl$** **525,11**		39 ± 1
PHD 230	**$C_{29}H_{32}N_2O_4S.HCl$** **541,11** **(122 °C)**		**65 ± 2**
PHD 235	**$C_{30}H_{34}N_2O_4S.HCl$** **555,14**		37 ± 5
PHD 242	**$C_{28}H_{29}ClN_2O_3S.HCl$** **545,53** **(141 °C)**		**60 ± 4**

Composé - (10 µM)	Formule brute - Masse molaire (point de fusion)	Structure	Accumulation d'(^{3}H)-IP % de la réponse 10mM Ca^{2+} ± ES
PHD 267	**$C_{29}H_{32}N_2O_4S.HCl$** **541,11**		45 ± 1
PHD 271	**$C_{29}H_{30}N_2O_5S.HCl$** **555,09**		47 ± 2
PHD 280	**$C_{22}H_{26}N_2O_3S.HCl$** **434,99**		30 ± 2
PHD 285	**$C_{28}H_{30}N_2.2HCl$** **467,49**		80 ± 8
PHD 288	**$C_{21}H_{24}N_2O_3S.HCl$** **420,99**		45 ± 3
PHD 301	**$C_{27}H_{27}N_2O_2SCl.HCl$** **515,50**		79 ± 10
PHD 304	**$C_{28}H_{27}F_3N_2O_2S.HCl$** **549,06**		29 ± 2

Composé - (10 μM)	Formule brute - Masse molaire (point de fusion)	Structure	Accumulation d'(^{3}H)-IP % de la réponse 10mM Ca^{2+} ± ES
PHD 306	$C_{28}H_{27}F_3N_2O_2S.HCl$ 549,06		48 ± 9
PHD 307	$C_{28}H_{29}ClN_2.2HCl$ 501,90 (129 °C)		98 ± 8
PHD 308	$C_{27}H_{27}N_2O_2SCl.HCl$ 515,50 (141-142 °C)		83 ± 4
PHD 312	$C_{28}H_{29}ClN_2.2HCl$ 501,90 (157-158 °C)		78 ± 6
PHD 316	$C_{25}H_{26}N_2O_2S.HCl$ 487,08		78 ± 1
PHD 317	$C_{22}H_{19}NO_2S$ 361,47		29 ± 13

Composé - (10 µM)	Formule brute - Masse molaire (point de fusion)	Structure	Accumulation d'(^{3}H)-IP % de la réponse 10mM Ca^{2+} ± ES
PHD 318	$C_{31}H_{30}N_2O_2S.HCl$ **531,12**		34 ± 2
PHD 319	$C_{31}H_{30}N_2O_2S.HCl$ **531,12**		31 ± 7
PHD 320	$C_{29}H_{29}FN_2.2HCl$ **485,47** (133 °C)		95 ± 4
PHD 321	$C_{29}H_{32}N_2O_4S.HCl$ **541,11** (186 °C)		97 ± 13
PHD 322	$C_{22}H_{26}N_2O_2S.HCl$ **418,99**		57 ± 6
PHD 323	$C_{29}H_{29}FN_2.2HCl$ **485,47** (141 °C)		90 ± 8

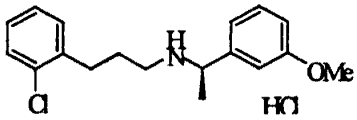
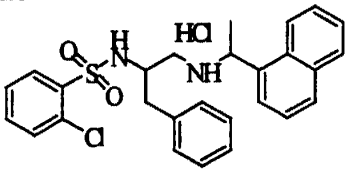
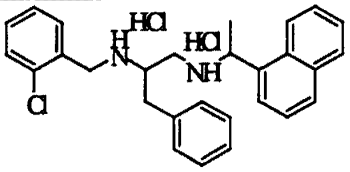
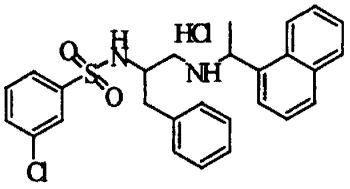
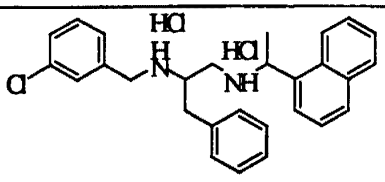
Ces exemples de composés et les résultats obtenus avec eux sont indiqués à titre non limitatif et illustrent l'invention.

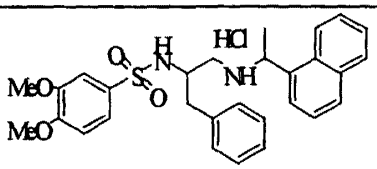
Spécificité de l'activité de ces molécules

Les molécules PHD, utilisées à une concentration de 10 µM ne conduisent pas ou peu à l'accumulation d'[^{3}H]IP dans des cellules CHO(WT*) témoins ce qui suggère leur spécificité d'action vis-à-vis du CaSR (Tableau 2). Les cellules CHO(WT*) ont été tranfectées avec le plasmide seul et n'expriment pas le CaSR.

L'accumulation d'inositols phosphates tritiés est exprimée en pourcentage du taux de base observé en présence de 2 mM Ca^{2+} (100 %) dans les cellules CHO(WT*) ou CHO(CaSR). Les composés PHD 301, 307, 308, 312 et 321 et NPS-R-568 induisent peu ou pas d'accumulation d'[^{3}H]IP dans les cellules CHO(WT*). Les composés PHD 301, 307, 308, 312, et 321 et NPS-R-568 induisent une forte accumulation d'[^{3}H]IP dans les cellules CHO(CaSR).

Tableau 2 : Accumulation d'inositols phosphates tritiés dans les cellules CHO(WT*) induite par les composés PHD et le composé calcimimétique NPS R-568

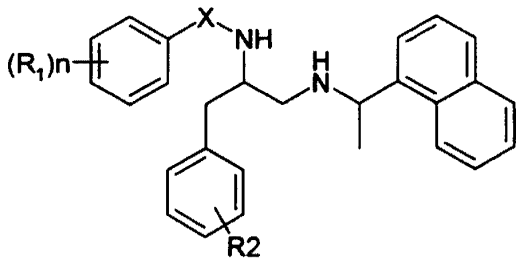
Composé - (10 □M)	Structure	Accumulation d'(^{3}H)-IP % du taux basal. CHO (WT*)	CHO (CaSR)
NPS R-568		119 ± 9	454 ± 33
PHD 301		119 ± 6	304 ± 18
PHD 307		134 ± 11	393 ± 28
PHD 308		124 ± 9	314 ± 13
PHD 312		121 ± 6	383 ± 39

Composé - (10 □M)	Structure	Accumulation d'(^{3}H)-IP % du taux basal. CHO (WT*)	CHO (CaSR)
PHD 321		124 ± 4	446 ± 22

Ces exemples de composés et les résultats obtenus avec eux sont indiqués à titre non limitatif et illustrent l'invention.

REVENDICATIONS

1. Arylalkyl-1,2-diamine de formule générale (I) :



I

dans laquelle :

le groupe X représente un groupe SO_2 ou CH_2,

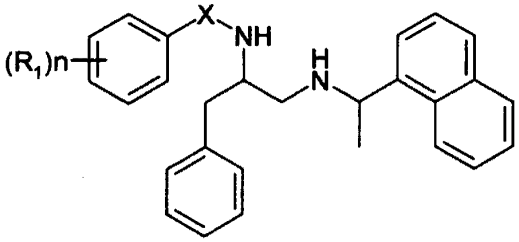
le groupe R1 représente un atome d'hydrogène ou d'halogène ou un groupe alkoxy, aryle, aralkyle ou un groupe alkyle substitué ou non par un ou plusieurs atomes d'halogènes,

n est égale à 0, 1 ou 2,

et le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy,

et leurs sel avec un acide pharmaceutiquement acceptable, sous forme de mélange racémique ou de leurs isomères optiquement purs.

2. Arylalkyl-1,2-diamine selon la revendication 1 caractérisé en ce qu'il est représenté par la formule générale (II) :



II

dans laquelle :

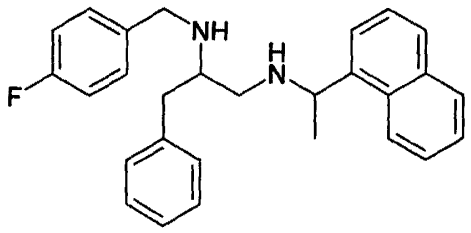
le groupe X représente un groupe SO_2 ou CH_2,

le groupe R1 représente un atome d'hydrogène ou d'halogène ou un groupe alkoxy, aryle, aralkyle ou un groupe alkyle substitué ou non par un ou plusieurs atomes d'halogènes,

et n est égale à 0, 1 ou 2.

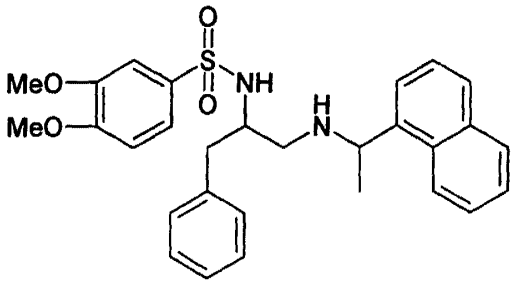
3. Arylalkyl-1,2-diamine selon les revendications 1 et 2 caractérisé en ce que le groupe R1 est un noyau benzo ou alkylbenzo fusionné

4. Arylalkyl-1,2-diamine selon les revendications 1 et 2 caractérisé en ce qu'il est représenté par la formule (III) :



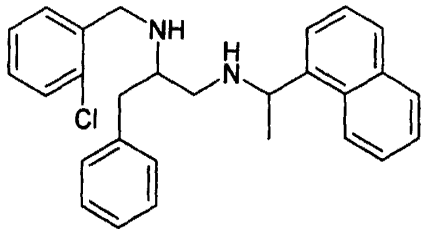
III

5. Arylalkyl-1,2-diamine selon les revendications 1 et 2 caractérisé en ce qu'il est représenté par la formule (IV) :



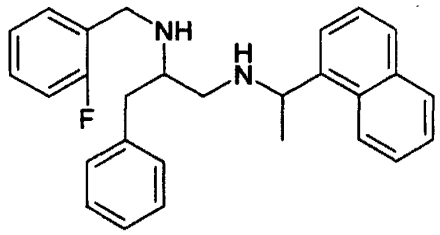
IV

6. Arylalkyl-1,2-diamine selon les revendications 1 et 2 caractérisé en ce qu'il est représenté par la formule (V) :



V

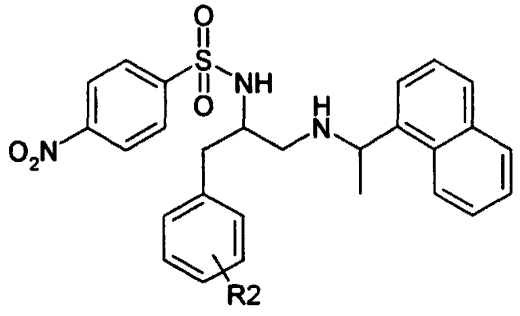
7. Arylalkyl-1,2-diamine selon les revendications 1 et 2 caractérisé en ce qu'il est représenté par la formule (VI) :



VI

8. Procédé de préparation des arylalkyl-1, 2-diamines de formule (I) dans laquelle X représente le groupe SO_2 selon les revendications 1 à 3 et 5 caractérisé en ce qu'il comporte les étapes suivantes :

a) le composé de formule (VII) :



VII

dans laquelle :

le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy

subit une réaction de déprotection

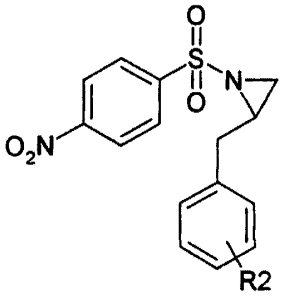
b) un groupement arylsulfonyle est introduit sélectivement sur une de ses fonctions amines du composé obtenu.

9. Procédé de préparation des arylalkyl-1,2-diamines de formule (I) dans laquelle X représente le groupe CH2 selon les revendications 1 à 4, 6 et 7 caractérisé en ce qu'il comporte les étapes suivantes :

a) un groupement arylbenzyle est introduit sélectivement sur une des fonctions amines du composé de formule (VII)

b) le composé obtenu subit une réaction de déprotection.

10. Procédé de préparation selon les revendications 8 et 9 caractérisé en ce que le composé de formule (VII) est obtenu par ouverture nucléophile par la 1-(1-naphtyl)éthylamine de la 2-benzyl-1-(*p*-nitrobenzènesulfonyl)aziridine de formule générale (VIII) :

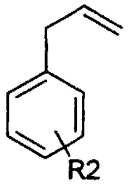


VIII

dans laquelle :

le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy.

11. Procédé de préparation selon les revendications 8 à 10 caractérisé en ce que le composé de formule (VIII) est obtenu par réaction entre une oléfine de formule générale (IX) :



IX

dans laquelle :

le groupe R2 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle ou alkoxy

et PhI=NSO_2Ph-*p*-NO_2 en présence de $Cu^{I\ ou\ II}$ et de CH_3CN.

12. Composition pharmaceutique comprenant un composé selon les revendications 1 à 7 et un support pharmaceutique approprié.

13. Utilisation des composés selon les revendications 1 à 7 et 12 comme modulateur de l'activité du CaSR

14. Utilisation selon la revendication 13 caractérisée en ce que le CaSR se trouve dans la glande parathyroïde, la thyroïde, les cellules osseuses, l'estomac, le poumon, le rein, l'hypophyse, le cerveau, l'hypothalamus, les aires olfactives ou l'hippocampe.

15. Utilisation selon les revendications 13 et 14 caractérisée en ce que ces composés sont plus sélectifs vis à vis des récepteurs de la parathyroïde comparativement à ceux de la glande thyroïde.

16. Composé selon les revendications 1 à 7 et 12 pour son utilisation comme médicament.

17. Utilisation des composés selon les revendications 1 à 7 et 12 pour la fabrication d'un médicament destiné au traitement des maladies ou des désordres physiologiques liés à des perturbations de l'activité des CaSR.

18. Utilisation selon la revendication 17 caractérisée en ce que les maladies ou les désordres physiologiques sont du type hyperparathyroïdies primaires ou secondaires, ostéoporose, maladies cardio-vasculaires, gastro-intestinales, endocrines, neurodégénératives ou certains cancers où les ions $(Ca^{2+})_e$ sont anormalement élevés.

19. Utilisation selon la revendication 18 caractérisée en ce que l'hyperparathyroïdie secondaire est observée lors d'insuffisance rénale chronique.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/FR 00/03104

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/18 C07C311/29 C07C211/30 A61K31/135 A61K31/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data, WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 41090 A (NPS PHARMACEUTICALS INC) 6 November 1997 (1997-11-06) * examples; revendications; figure 1 composé 6X *	1,12-19
A	P. E. MALIGRES ET AL: TETRAHEDRON LETT., vol. 38, no. 30, 1997, pages 5253-5256, XP004083291 the whole document	10

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2001	16/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/FR 00/03104

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9741090 A	06-11-1997	AU 2822997 A	19-11-1997
		CA 2253407 A	06-11-1997
		EP 0907631 A	14-04-1999
		JP 2000509395 T	25-07-2000
		US 5981599 A	09-11-1999

Form PCT/ISA/210 (patent family annex) (July 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale No
PCT/FR 00/03104

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 7 C07C311/18 C07C311/29 C07C211/30 A61K31/135 A61K31/18

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 7 C07C A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)
CHEM ABS Data, BEILSTEIN Data, WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	WO 97 41090 A (NPS PHARMACEUTICALS INC) 6 novembre 1997 (1997-11-06) * examples; revendications; figure 1 composé 6X *	1,12-19
A	P. E. MALIGRES ET AL: TETRAHEDRON LETT., vol. 38, no. 30, 1997, pages 5253-5256, XP004083291 le document en entier	10

☐ Voir la suite du cadre C pour la fin de la liste des documents

☒ Les documents de familles de brevets sont indiqués en annexe

° Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
9 février 2001	16/02/2001

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Amsterdam, L

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Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No
PCT/FR 00/03104

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
WO 9741090 A	06-11-1997	AU 2822997 A	19-11-1997
		CA 2253407 A	06-11-1997
		EP 0907631 A	14-04-1999
		JP 2000509395 T	25-07-2000
		US 5981599 A	09-11-1999

Formulaire PCT/ISA/210 (annexe familles de brevets) (juillet 1992)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 933 354 A1

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(51) Int. Cl.[6]: **C07C 211/30**, C07C 211/29, C07C 211/27, C07C 217/14, C07C 225/16, C07C 237/04, C07C 323/23, C07C 317/26, C07D 209/08, C07D 209/12, C07D 209/14

(86) International application number:
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(54) CALCIUM RECEPTOR-ACTIVE COMPOUNDS

(57) A novel calcium receptor active compound having the formula is provided:

Ar_1-[CR^1 R^2]$_p$-X-[CR^3R^4]$_q$-[CR^5R^6]-NR^7-[CR^8R^9]-Ar_2

wherein:

Ar_1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl)amino;
X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are, for example, hydrogen or alkyl;
Ar_2 is selected from the group consisting of aryl and heteroaryl;
p is an integer of from 0 to 6, inclusive; and,
q is an integer of from 0 to 14, inclusive.

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Description

Field of the Invention

[0001] This invention relates to the design, development, composition and use of novel molecules able to modulate the activity of inorganic ion receptor.

Background of the Invention

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

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

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

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

[0006] The ability of various compounds to mimic extracellular Ca^{2+} in vitro is discussed by Nemeth et al., (spermine and spermidine) in "Calcium-Binding Proteins in Health and Disease", 1987, Academic Press, Inc., pp. 33-35; Brown et al., (e.g., neomycin) 128 Endocrinology 3047, 1991; Chen et al., (diltiazem and its analog, TA-3090) 5 J. Bone and Mineral Res. 581, 1990; and Zaidi et al., (verapamil) 167 Biochem. Biophys. Res. Commun. 807, 1990 Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959, Nemeth et al., PCT/US92/07175, International Publication Number WO 93/04373, Nemeth et al., PCT/US94/12117, International Publication Number WO 95/11221 and Nemeth et al., PCT/US95/13704, International Publication Number WO 96/12697 describe various compounds which can modulate the effect of an inorganic ion on a cell having an inorganic ion receptor, preferably modulate the effects of calcium on a calcium receptor.

[0007] The object of the present invention is to provide a novel inorganic ion receptor active compound having the structure different from the compounds described above.

Disclosure of the Invention

[0008] The present invention features molecules which can modulate one or more activities of an inorganic ion receptor. Preferably, the molecule can mimic or block the effect of extracellular Ca^{2+} on a calcium receptor. The preferred use of such molecules is to treat diseases or disorders by altering inorganic ion receptor activity, preferably calcium receptor activity.

[0009] The present invention provides a novel calcium receptor active compound of the formula:

$$Ar_1\text{-}[CR^1R^2]_p\text{-}X\text{-}[CR^3R^4]_q\text{-}[CR^5R^6]\text{-}NR^7\text{-}[CR^8R^9]\text{-}Ar_2 \quad (1)$$

wherein:

Ar_1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl)amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;

R^1 R^2, R^3, R^4, R^5, R^6, R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, trihalomethyl, aryl, heteroaryl, heteroalicyclic, halogen, hydroxy, alkoxy, thioalkoxy, aryloxy, thioaryloxy, carbonyl, thiocarbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, O-carbamyl, N-carbamyl, O-

thiocarbamyl, N-thiocarbamyl, cyano, nitro, amino and $NR^{10}R^{11}$; wherein,

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, carbonyl, trihaloacetyl, sulfonyl, trihalomethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen;

any two adjacent "R" groups may be combined to form five- or six-member fused cycloalkyl groups;

R^7 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, halogen, cyano, hydroxy, alkoxy, O-carboxyl, trihaloacetyl and trihalomethanesulfonyl;

Ar_2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive;

or a pharmaceutically acceptable salt or hydrate of said compound.

[0010] As used herein, the term "aryl" refers to an all-carbon monocyclic or fused ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups in which one or more of the rings has a completely conjugated pi-electron system. Examples, without limitation, of aryl groups, are phenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, and indanyl. The aryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more selected from halogen, trihalomethyl, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethanesulfonamido, amino and $NR^{10}R^{11}$ wherein:

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl, trihalomethanesulfonyl, and, combined, a five- or six-member heteroalicyclic ring which heteroalicyclic ring may be unsubstituted or substituted with one or more halogens.

[0011] A "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, at least one of the rings has a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups are pyrrole, furan, dibenzofuran, carbazole, acridine, thiophene, imidazole, benzimidazole, oxazole, thiazole, phenothiazine, triazole, thiadiazole, pyrazole, benzoxazole, benzthiazole, indole, benzofuran, indazole, pyridine, pyrimidine, quinoline, isoquinoline, quinazoline, purine, phthalazine and flavone. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, halogen, trihalomethyl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, carbonyl, thiocarbonyl, sulfonamido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, trihalomethanesulfonamido, amino and $NR^{10}R^{11}$ where R^{10} and R^{11} are previously defined herein.

[0012] As used herein, the term "alkyl" refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms. More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, halogen, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, C-carboxy, O-carboxy, nitro, sulfonamido, trihalomethanesulfonamido, amino and $NR^{10}R^{11}$ where R^{10} and R^{11} are previously defined herein. More preferably, the alkyl group is a medium or lower alkyl which is optionally substituted with one or more groups independently selected from halogen, hydroxy, nitro, cyano and unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens; an unsubstituted lower alkyl; and a lower alkyl substituted with one or more halogens.

[0013] A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein none of the rings has a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, cycloheptane and, cycloheptatriene. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalycyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, halogen, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, O-carbamyl, N-carbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, amino and $NR^{10}R^{11}$, where R^{10} and R^{11} are previously defined herein. Preferably the cycloalkyl group is selected from unsubstituted cyclopropane, unsubstituted cyclopentane, unsubstituted cyclohexane, and cyclopropane, cyclopentane and cyclohexane substituted with one or more groups independently selected from halogen, nitro, cyano, hydroxy, unsubstituted lower alkoxy, C-carboxyl wherein R" is unsubstituted lower alkyl and O-carboxyl wherein R" is unsubstituted lower alkyl.

[0014] An "alkenyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. A "lower alkenyl" group refers to a lower alkyl group containing at least one double bond.

[0015] A "cycloalkenyl" group refers to a cycloalkyl group which contains one or more double bonds in the ring wherein the double bonds do not produce a completely conjugated pi-electron system within the ring.

[0016] An "alkynyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. A "lower alkynyl" group refers to a lower alkyl group containing at least one triple bond.

[0017] A "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, none of the rings has a completely conjugated pi-electron system. The heteroalicyclic ring may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, halogen, trihalomethyl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, C-amido, N-amido, amino and $NR^{10}R^{11}$ where R^{10} and R^{11} are previously defined herein.

[0018] A "phenyl" group refers to a six-member ring aryl group.

[0019] A "benzyl" group refers to a phenyl-CH_2- group.

[0020] A "hydroxy" group refers to an -OH group.

[0021] An "alkoxy" group refers to both an -O-alkyl and an -O-cycloalkyl group, as defined herein; preferably an alkoxy group refers to a methoxy or trihalomethoxy.

[0022] A "trihalomethoxy" group refers to a Y_3CO- group with Y as defined herein; preferably Y is fluorine.

[0023] A "benzyloxy" refers to a benzyl-O- group.

[0024] An "aryloxy" group refers to both an -O-aryl and an -O-heteroaryl group, as defined herein. A "phenoxy" group refers to an aryloxy group in which the aryl group is a phenyl group. A "thiohydroxy" group refers to an -SH group.

[0025] A "thioalkoxy" group refers to both an S-alkyl and an -S-cycloalkyl group, as defined herein.

[0026] A "thioaryloxy" group refers to both an -S-aryl and an -S-heteroaryl group, as defined herein.

[0027] A "carbonyl" or "acyl" group refers to a -C(=O)-R" group, where R" is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as defined herein.

[0028] An "formyl" group refers to a carbonyl group wherein R" is hydrogen.

[0029] An "acetyl" group refers to a carbonyl group wherein R" is CH_3.

[0030] A "thiocarbonyl" group refers to a -C(=S)-R" group, with R" as defined herein.

[0031] A "trihalomethyl" group refers to a $-CY_3$ group wherein Y is a halogen group; preferably Y is fluorine.

[0032] A "trihaloacetyl" group refers to a $Y_3CC(=O)$- group with Y as defined herein.

[0033] A "C-carboxyl" group refers to a -C(=O)O-R" groups, with R" as defined herein.

[0034] An "O-carboxyl" group refers to a R"C(=O)O- group, with R" as defined herein.

[0035] An "acetoxy" group refers to an O-carboxyl group in which R" is CH_3.

[0036] A "carboxylic acid" group refers to a C-carboxyl group in which R" is hydrogen.

[0037] A "halo" or "halogen" group refers to fluorine, chlorine, bromine or iodine.

[0038] A "trihalomethanesulfonyl" group refers to a $Y_3CS(=O)_2$- groups with Y as defined above.

[0039] A "trihalomethanesulfonamido" group refers to a $Y_3CS(=O)_2NR^{10}$- group with Y and R^{10} as defined herein.

[0040] A "sulfinyl" group refers to a -S(=O)-R" group, with R" as defined herein or R" may not exist if both S-bonds are already in use internally in a particular molecule.

[0041] A "sulfonyl" group refers to a $-S(=O)_2R$" group, with R" as defined herein or R" may not exist is both S-bonds are already in use internally in an particular molecule.

[0042] An "S-sulfonamido" group refers to a $-S(=O)_2NR^{10}R^{11}$ with R^{10} and R^{11} as defined herein.

[0043] An "N-sulfonamido" group refers to a $R^{10}S(=O)_2NR^{11}$- group, with R^{10} and R^{11} as defined herein.

[0044] An "O-carbamyl" group refers to a $-OC(=O)NR^{10}R^{11}$ group with R^{10} and R^{11} as defined herein..

[0045] An "N-carbamyl" group refers to a $R^{10}OC(=O)NR^{11}$- group, with R^{10} and R^{11} as defined herein.

[0046] An "O-thiocarbamyl" group refers to a $-OC(=S)NR^{10}R^{11}$ group with R^{10} and R^{11} as defined herein.

[0047] An "N-thiocarbamyl" group refers to a $R^{10}OC(=S)NR^{11}$- group, with R^{10} and R^{11} as defined herein.

[0048] An "amino" group refers to an $-NR^{10}R^{11}$ group, with R^{10} and R^{11} as defined herein.

[0049] A "C-amido" group refers to a $-C(=O)NR^{10}R^{11}$ group with R^{10} and R^{11} as defined herein.

[0050] An "N-amido" group refers to a $R^{10}C(=O)NR^{11}$- group, with R^{10} and R^{11} as defined herein.

[0051] A "nitro" group refers to a $-NO_2$ group.

[0052] A "methylenedioxy" group refers to a $-OCH_2O$- group in which the two oxygens are covalently bonded to adjacent carbon atoms of an aryl or heteroaryl group.

[0053] An "ethylenedioxy" group refers to a $-OCH_2CH_2O$- groups in which the two oxygens are covalently bonded to

adjacent carbon atoms of an aryl or heteroaryl group.

[0054] Preferably, in the formula (1), R^5 is selected from the group consisting of hydrogen, unsubstituted lower alkyl and lower alkyl substituted with one or more halogens; R^1, R^2, R^3,R^4, R^5 ,R^6 and R^7 are hydrogen; and R^8 and R^9 are independently selected from the group consisting of hydrogen, unsubstituted alkyl, lower alkyl substituted with one or more halogens, unsubstituted alkenyl, lower alkenyl substituted with one or more halogens, unsubstituted alkynyl, alkynyl substituted with one or more halogens and, combined, unsubstituted cycloalkyl and cycloalkenyl. Also preferably, Ar_1 is selected from the group consisting of phenyl, naphthyl, indolyl, fluorenyl, dibenzofuranyl, carbazolyl, benzoxazole-2-yl, benzthiazole-2-yl, pyridin-4-yl, quinolin-2-yl and dibenzylamino and Ar_2 is selected from the group consisting of phenyl, naphthyl, quinolin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrrol-2-yl and pyrrol-3-yl. More preferably, Ar_1 is phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, halogen, trihalomethyl, unsubstituted lower alkoxy, trihalomethoxy, trihaloacetyl and nitro, and Ar_2 is selected from the group consisting of optionally substituted phenyl and optionally substituted naphthyl. Even more preferably, Ar_2 is 3-methoxyphenyl or unsubstituted naphthyl. Preferably, R^8 is hydrogen, R^9 is methyl and X is oxygen or sulfur.

[0055] In another aspect, the present invention provides a compound of the formula:

$$Ar_3\text{-}(CHR^{12})_r\text{-}Q\text{-}(CH_2)_s\text{-}CHR^{13}\text{-}NH\text{-}CR^{14}R^{15}\text{-}Ar_4 \qquad (2)$$

wherein:

Ar_3 is selected from the group consisting of aryl and heteroaryl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkenyl, lower alkenyl substituted with one or more halogens, halogen, hydroxy, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, unsubstituted lower thioalkoxy, nitro, formyl, acetoxy, acetyl, $-CH_2OH$, $CH_3CH(OH)$-, $-C(=O)NH_2$, cyano, -N(lower alkyl)$_2$, phenyl, phenoxy, benzyl, benzyloxy, methylenedioxy, ethylenedioxy, α, α-dimethylbenzyl, and $-OCH_2COOH$;
Ar_4 is selected from the group consisting of aryl and heteroaryl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkenyl, lower alkenyl substituted with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, hydroxy, lower thioalkoxy, halogen, methylenedioxy, ethylenedioxy, acetoxy, $-OCH_2COOH$, $-C(=O)NH_2$, cyano, and $-CH_2OH$;
r is an integer of from 0 to 6, inclusive;
s is an integer of from 0 to 14, inclusive;
Q is selected from the group consisting of oxygen, sulfur, carbonyl and -NH-;
R^{13} is hydrogen or lower alkyl; and
R^{14} and R^{15} are independently selected from the group consisting of hydrogen, alkyl and, combined, cycloalkyl and cycloalkenyl;
or a pharmaceutically acceptable salt or hydrate of said compound.

[0056] Preferably, in the formula (2), Ar_3 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and optionally substituted naphthyl; and Ar_4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and optionally substituted naphthyl.

[0057] In another aspect, the present invention provides a compound of the formula:

$$Ar_5\text{-}(CHR^{16})_t\text{-}W\text{-}(CH_2)_u\text{-}CHR^{17}\text{-}NH\text{-}CH(R^{18})\text{-}Ar_6 \qquad (3)$$

wherein:

Ar_5 is aryl, dicyclic or tricyclic heteroaryl, arylmethyl(arylmethyl)amino, heteroarylmethy(heteroarylmethyl)amino or arylmethyl(heteroarylmethyl)amino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, unsubstituted lower alkenyl, halogen, hydroxy, unsubstituted lower alkoxy, unsubstituted lower thioalkoxy, lower alkyl substituted with one or more halogens, lower alkenyl substituted with one or more halogens, lower alkoxy substituted with one or more halogens, nitro, formyl, acetoxy, acetyl, $-CH_2OH$, $CH_3CH(OH)$-, $-C(=O)NH_2$, cyano, -N(unsubstituted lower alkyl)$_2$, phenyl, phenoxy, benzyl, benzyloxy, α, α

-dimethylbenzyl, methylenedioxy, ethylenedioxy and -OCH_2COOH;

Ar_6 is aryl or dicyclic or tricyclic heteroaryl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkenyl, lower alkenyl substituted with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, halogen, hydroxy, unsubstituted lower thioalkoxy, lower thioalkoxy substituted with one or more halogens, benzyloxy, methylenedioxy, ethylenedioxy, acetoxy, -OCH_2COOH, -$C(=O)NH_2$, cyano, and -CH_2OH;

t is 0 or 1;

u is an integer of from 0 to 11, inclusive;

W is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;

R^{16} and R^{17} are H or unsubstituted lower alkyl; and

R^{18} is unsubstituted lower alkyl;

or a pharmaceutically acceptable salt or hydrate of said compound.

[0058] Preferably, in the formula (3), Ar_5 is phenyl, indole, benzothiazole, benzoxazole, dibenzofuran, carbazole, pyridine, fluorene, quinoline, naphthalene, chromenone, tetrahydrobenzothiazepine, dibenzylamino, benzyl(naphthylmethyl)amino, benzyl(pyridylmethyl)amino, thienylmethyl(benzyl)amino, furylmethyl(benzyl)amino or N-alkylpyrrolylmethyl(benzyl)amino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl; and Ar_6 is thiophene, furan, pyrrole, phenyl, naphthalene, pyridine, pyrazine or thiazole optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens, lower alkoxy substituted with one or more halogens, hydroxy and benzyloxy optionally substituted with halogen or methyl. More preferably, Ar_5 is selected from the group consisting of phenyl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens; and Ar_6 is 3-methoxyphenyl or α-naphthyl, more preferably, α-naphthyl. Also preferably, Ar_5 is dibenzylamino, benzyl(naphthylmethyl)amino or benzyl(pyridylmethyl)amino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens, and Ar_6 is naphthyl or methoxyphenyl. More preferably, Ar_5 is dibenzylamino optionally substituted with unsubstituted alkyl, and Ar_6 is α-naphthyl.

[0059] Preferably, the compound of the present invention represented by the formulae (1), (2) or (3) is the R enantiomer. The present invention also provides a prodrug of any of the compounds described above.

[0060] The present invention provides a method for modulating calcium receptor activity by using a compound described herein. The featured compounds preferably modulate an interaction of Ca^{2+} with Ca^{2+} receptors by mimicking (including potentiating) the effect of Ca^{2+} on a Ca^{2+} receptor (calcimimetic modulation) or blocking the effect of Ca^{2+} on a Ca^{2+} receptor (calcilytic modulation); preferably calcimimetic modulation.

[0061] Also provided is a method for the treatment in a patient of disorders characterized by an abnormal concentrations of one or more inorganic ions or other physiological biochemical substances, the concentration of which is regulated by an activity of one or more calcium receptors. In particular, treatment using the compounds disclosed hereof is contemplated for disorders characterized by abnormal extracellular Ca^{2+} concentration ($[Ca^{2+}]$) or abnormal intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in one or more cells including for example, but without limitation, parathyroid cells, bone osteoclasts, juxtaglomerular kidney cells, proximal tubule kidney cells, keratinocytes, parafollicular thyroid cells and placental trophoblasts.

[0062] An "abnormal" state is characterized by a level of a property that is statistically different from the level of that property observed in patients not suffering from a particular disorder. Thus, for example, the term "abnormal" as it relates to inorganic ion concentrations refers to a concentration of the ion in question which would be recognized by members of the medical community as being outside the normal range of such ion concentration in healthy patients.

[0063] As used herein, the terms "treat", "treating" and "treatment" refer to a method of alleviating, abrogating, and/or having a prophylactic effect with regard to, a disease or disorder and/or one or more, preferably all, its attendant symptoms.

[0064] In another aspect, the present invention provides a method for the treatment or prevention of primary and secondary hyperparathyroidism, renalosteodystrophy, hypercalcemia malignancy, osteoporosis, Paget's disease and hypertension comprising administering a therapeutically effective amount of a compound of this invention to a patient.

[0065] The term "administering" as used herein refers to a method for introducing a compound of this invention in vitro or in vivo. Thus, for example, the importance of inorganic ion receptor activity can be studied and associated diseases and disorders prevented or treated by the compounds and methods set forth herein. Cells existing outside the organism

can be maintained or grown in cell culture dishes. In this context, the ability of a particular compound to affect an inorganic ion receptor activity can be determined; i.e., the IC50 or EC50, preferably the EC50, of a compound, defined below, before the use of the compounds in complex multicellular living organisms such as a human is attempted. For cells outside the organism, multiple methods exist, and are well-known to those skilled in the arts, to administer compounds including, but not limited to, cell micro-injection, transformation and numerous carrier techniques.

[0066] For cells harbored within a multicellular living organism, myriad methods also exist, and are likewise well-known to those skilled in the art, to administer compounds including, but not limited to, oral, parenteral, dermal, injection and aerosol applications.

[0067] The present invention features a method for the modulation of one or more activities of an inorganic ion receptor using the compounds disclosed herein. Preferably, the inorganic ion receptor is a Ca^{2+} receptor. The compounds of this invention can either mimic (including potentiation) or block the effect of extracellular Ca^{2+} on a calcium receptor. The preferred use of such compounds is to treat selected disorders by modulating the inorganic ion receptor activity. In particular the compounds of this invention can be used to treat the indicated disorders by modulating Ca^{2+} receptor activity.

[0068] Extracellular Ca^{2+} is under tight homeostatic control and controls various processes such as blood clotting, nerve and muscle excitability, and proper bone formation. Calcium receptor proteins enable certain specialized cells to respond to changes in extracellular Ca^{2+} concentration. For example, extracellular Ca^{2+} inhibits the secretion of parathyroid hormone from parathyroid cells, inhibits bone resorption by osteoclasts, and stimulates secretion of calcitonin from C-cells.

[0069] Compounds modulating inorganic ion receptor activity can be used to treat diseases or disorders by affecting one or more activities of an inorganic ion receptor resulting in a beneficial effect to the patient. For example, osteoporosis is an age related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds blocking osteoclastic bone resorption either directly (e.g., a osteoclast ionmimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell ionmimetic), and/or by decreasing parathyroid hormone levels (e.g., a parathyroid cell ionmimetic) can retard bone loss and, thus, result in beneficial effects to patients suffering from osteoporosis.

[0070] In addition, it is known that intermittent low dosing with PTH results in an anabolic effect on bone mass and appropriate bone remodeling. Thus, compounds and dosing regiments evoking transient increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionlytic) can increase bone mass in patients suffering from osteoporosis.

[0071] Additionally, diseases or disorders characterized by a defect in one or more inorganic ion receptor activities may be treated by the present invention. For example, certain forms of primary hyperparathyroidism are characterized by abnormally high levels of parathyroid hormone and decreased parathyroid gland responsiveness to circulating calcium. Calcium receptor modulating agents can be used to modulate parathyroid cell responsiveness to calcium.

[0072] Preferably, the compound modulates calcium receptor activity and is used in the treatment of diseases or disorders which can be affected by modulating one or more activities of a calcium receptor. Preferably, the disease or disorder is characterized by abnormal bone and mineral homeostasis, more preferably calcium homeostasis.

[0073] Abnormal calcium homeostasis is characterized by one or more of the following activities: (1) an abnormal increase or decrease in serum calcium; (2) an abnormal increase or decrease in urinary excretion of calcium; (3) an abnormal increase or decrease in bone calcium levels, for example, as assessed by bone mineral density measurements; (4) an abnormal absorption of dietary calcium; and (5) an abnormal increase or decrease in the production and/or release of circulating messengers or hormones which affect calcium homeostasis such as parathyroid hormone and calcitonin. The abnormal increase or decrease in these different aspects of calcium homeostasis is relative to that occurring in the general population and is generally associated with a disease or disorder.

[0074] More generally, a molecule which modulates the activity of an inorganic ion receptor is useful in the treatment of diseases characterized by abnormal inorganic ion homeostasis. Preferably, the molecule modulates one or more effects of an inorganic ion receptor. Inorganic ion receptor modulating agents include ionmimetics, ionlytics, calcimimetics, and calcilytics.

[0075] Ionmimetics are molecules which mimic the effects of increasing ion concentration at an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. Calcimimetics are ionmimetics which affect one or more calcium receptor activities and preferably binds to a calcium receptor.

[0076] Ionlytics are molecules which reduce or block one or more activities caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule inhibits one or more calcium receptor activities. Calcilytics are ionlytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and preferably bind to a calcium receptor.

[0077] Inorganic ion receptor modulating agents can be formulated as pharmacological agents or compositions to facilitate administration in a patient. Pharmacological agents or compositions are agents or compositions in a form suitable for administration into a mammal, preferably a human. considerations concerning forms suitable for administration are known in the art and include toxic effects, solubility, route of administration, and maintaining activity.

[0078] Other aspects of the present invention feature methods for using the agents described herein for treating diseases or disorders by modulating inorganic ion receptor activity. Patients in need of such treatments can be identified by standard medical techniques, such as routine blood analysis. For example, by detecting a deficiency of protein whose production or secretion is affected by changes in inorganic ion concentrations, or by detecting abnormal levels of inorganic ions or hormones which effect inorganic ion homeostasis.

[0079] Therapeutic methods involve administering to the patient a therapeutically effective amount of an inorganic ion receptor modulating agent. In preferred embodiments these methods are used to treat a disease or disorder characterized by abnormal inorganic ion homeostasis, more preferably a disease or disorder characterized by abnormal calcium homeostasis. Diseases and disorders characterized by abnormal calcium homeostasis include hyperparathyroidism, osteoporosis, renalosteodystrophy and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's Principles of Internal Medicine"). Such diseases and disorders are treated using calcium receptor modulating agents which mimic or block one or more of the effects of Ca^{2+} and, thereby, directly or indirectly affect the levels of proteins or other molecules in the body of the patient.

[0080] By "therapeutically effective amount" is meant an amount of an agent which relieves to some extent one or more symptoms of the disease or disorder in the patient; or returns to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of the disease or disorder.

[0081] In a preferred embodiment, the patient has a disease or disorder characterized by an abnormal level of one or more calcium receptor regulated components and the molecule is active on a calcium receptor of a cell selected from the group consisting of parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, trophoblast in the placenta, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell and GI tract cell.

[0082] More preferably, the cell is a parathyroid cell and the molecule reduces the level of parathyroid hormone in the serum of the patient, even more preferably the level is reduced to a degree sufficient to cause a decrease in plasma Ca^{2+}, most preferably the parathyroid hormone level is reduced to that present in a normal individual.

[0083] Thus, the present invention features agents and methods useful in the treatment of diseases and disorders by modulating inorganic ion receptor activity. For example, the molecules of the present invention can be used to target calcium receptors on different cell types that detect and respond to changes to external calcium. For example, molecules mimicking external calcium may be used to selectively depress secretion of parathyroid hormone from parathyroid cells, or depress bone resorption by osteoclasts, or stimulate secretion of calcitonin from C-cells. Such molecules can be used to treat diseases or disorders characterized by abnormal calcium homeostasis such as hyperparathyroidism, renalosteodystrophy and osteoporosis.

[0084] Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof and from the claims.

Brief Description of Drawings

[0085]

Fig. 1 shows the structures of the compounds of the present invention synthesized in Examples 1 to 23.

Fig. 2 shows the scheme of the synthesis of the compound of the present invention of the formula (1) wherein X is O.

Fig. 3 shows the scheme of the synthesis of the compound of the present invention of the formula (1) wherein X is S.

Fig. 4 shows the scheme of the synthesis of the compound of the present invention of the formula (1) wherein Ar_1 is benzothiazole or benzoxazole.

Fig. 5 shows the structures of the compounds of the present invention synthesized in Examples 24 to 26 and the scheme of the synthesis thereof.

Fig. 6 shows the structures of the compounds of the present invention synthesized in Examples 27 to 32 and the scheme of the synthesis thereof.

Fig. 7 shows the structures of the compounds of the present invention synthesized in Examples 33 to 36 and the scheme of the synthesis thereof.

Fig. 8 shows the structures of the compounds of the present invention synthesized in Examples 37 to 40 and the scheme of the synthesis thereof.

Fig. 9 shows the structures of the compounds of the present invention synthesized in Examples 41 and 42 and the scheme of the synthesis thereof.

Fig. 10 shows the structures of the compounds of the present invention synthesized in Examples 43 to 56.

Fig. 11 shows the structures of the compounds of the present invention synthesized in Examples 57 to 70.
Fig. 12 shows the structures of the compounds of the present invention synthesized in Examples 71 to 84.
Fig. 13 shows the structures of the compounds of the present invention synthesized in Examples 85 and 86.
Fig. 14 shows the structure of the compound of the present invention synthesized in Example 88 and the scheme of the synthesis thereof.
Fig. 15 shows the structures of the compounds of the present invention synthesized in Examples 89 and 90.
Fig. 16 shows the structure of the compound of the present invention synthesized in Examples 91 to 93 and the scheme of the synthesis thereof.
Fig. 17 shows the structures of the compounds of the present invention synthesized in Examples 94 to 96 and the scheme of the synthesis thereof.
Fig. 18 shows the structures of the compounds of the present invention synthesized in Examples 97 to 100 and the scheme of the synthesis thereof.
Fig. 19 shows the structures of the compounds of the present invention synthesized in Examples 101 to 103 and the scheme of the synthesis thereof.
Fig. 20 shows the structures of the compounds of the present invention synthesized in Examples 104 to 106 and the scheme of the synthesis thereof.
Fig. 21 shows the structures of the compounds of the present invention synthesized in Examples 107 to 109 and the scheme of the synthesis thereof.
Fig. 22 shows the structures of the compounds of the present invention synthesized in Examples 110 to 112 and the scheme of the synthesis thereof.
Fig. 23 shows the structures of the compounds of the present invention synthesized in Examples 113 to 115 and the scheme of the synthesis thereof.
Fig. 24 shows the structures of the compounds of the present invention synthesized in Examples 116 to 118 and the scheme of the synthesis thereof.
Fig. 25 shows the structures of the compounds of the present invention synthesized in Examples 119 to 121 and the scheme of the synthesis thereof.
Fig. 26 shows the structures of the compounds of the present invention synthesized in Examples 122 to 134.
Fig. 27 shows the structures of the compounds of the present invention synthesized in Examples 135 to 147.
Fig. 28 shows the structures of the compounds of the present invention synthesized in Examples 148 to 189.
Fig. 29 shows the structures of the compounds of the present invention synthesized in Examples 190 to 231.
Fig. 30 shows the structures of the compounds of the present invention synthesized in Examples 232 to 271.
Fig. 31 shows the structures of the compounds of the present invention synthesized in Examples 272 to 313.
Fig. 32 shows the structures of the compounds of the present invention synthesized in Examples 314 to 355.
Fig. 33 shows the structures of the compounds of the present invention synthesized in Examples 356 to 387.
Fig. 34 shows the structures of the compounds of the present invention synthesized in Examples 388 to 407.
Fig. 35 shows the structures of the compounds of the present invention synthesized in Examples 408 to 413.
Fig. 36 shows the structures of the compounds of the present invention synthesized in Examples 416 to 428.
Fig. 37 shows the structures of the compounds of the present invention synthesized in Examples 429 to 441.
Fig. 38 shows the structures of the compounds of the present invention synthesized in Examples 442 to 455.
Fig. 39 shows the structures of the compounds of the present invention synthesized in Examples 456 to 469.
Fig. 40 shows the structures of the compounds of the present invention synthesized in Examples 470 to 480.
Fig. 41 shows the structures of the compounds of the present invention synthesized in Examples 481 to 490.
Fig. 42 shows the structures of the compounds of the present invention synthesized in Examples 491 to 495.
Fig. 43 shows the structures of the compounds of the present invention synthesized in Examples 496 to 504.
Fig. 44 shows the structures of the compounds of the present invention synthesized in Examples 505 to 517.
Fig. 45 shows the structures of the compounds of the present invention synthesized in Examples 518 to 529.
Fig. 46 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2027 was administered.
Fig. 47 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2052 was administered.
Fig. 48 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2076 was administered.
Fig. 49 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2087 was administered.
Fig. 50 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2117 was administered.
Fig. 51 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2240 was administered.

Fig. 52 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2243 was administered.

Fig. 53 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2246 was administered.

Fig. 54 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2247 was administered.

Fig. 55 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2250 was administered.

Fig. 56 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2257 was administered.

Fig. 57 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2259 was administered.

Fig. 58 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2262 was administered.

Fig. 59 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2263 was administered.

Fig. 60 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2264 was administered.

Fig. 61 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2265 was administered.

Fig. 62 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2266 was administered.

Fig. 63 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2267 was administered.

Fig. 64 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2269 was administered.

Fig. 65 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2270 was administered.

Fig. 66 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2271 was administered.

Fig. 67 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2272 was administered.

Fig. 68 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2279 was administered.

Fig. 69 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2280 was administered.

Fig. 70 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2281 was administered.

Fig. 71 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2282 was administered.

Fig. 72 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2283 was administered.

Fig. 73 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2284 was administered.

Fig. 74 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2286 was administered.

Fig. 75 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2287 was administered.

Fig. 76 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2288 was administered.

Fig. 77 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2289 was administered.

Fig. 78 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2290 was administered.

Fig. 79 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2291 was administered.

Fig. 80 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2292 was administered.

Fig. 81 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2293 was administered.

Fig. 82 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2294 was administered.

Fig. 83 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2296 was administered.

Fig. 84 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2297 was administered.

Fig. 85 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2298 was administered.

Fig. 86 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2299 was administered.

Fig. 87 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2300 was administered.

Fig. 88 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2301 was administered.

Fig. 89 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2302 was administered.

Fig. 90 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2303 was administered.

Fig. 91 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2304 was administered.

Fig. 92 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2305 was administered.

Fig. 93 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2309 was administered.

Fig. 94 shows changes in the plasma Ca^{2+} level of the rats to which the compound of the present invention K-2310 was administered.

Fig. 95 shows changes in the serum PTH level of the rats to which the compound of the present invention K-2076, K-2117 or K-2259 was administered.

Fig. 96 shows relative changes in the serum PTH level of the rats to which the compound of the present invention K-2076, K-2117 or K-2259 was administered to the pre-administration level.

Preferred Embodiments of the Invention

[0086] The present invention describes inorganic ion receptor modulating agents able to mimic or block an effect of an inorganic ion at an inorganic ion receptor. The preferred use of inorganic ion receptor modulating agents is to treat a disease or disorder by modulating inorganic ion receptor activity. Preferably, the molecules are used to treat diseases or disorders characterized by abnormal ion homeostasis, more preferably abnormal calcium homeostasis. Other uses of inorganic ion receptor modulating agents, such as diagnostics uses, are known in the art. Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.

I. CALCIUM RECEPTORS

[0087] Calcium receptors and nucleic acid encoding calcium receptors are described by Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959. Calcium receptors are present on different cell types such as parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, trophoblast in the placenta, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell, and GI tract cell. The calcium receptor on these cell types may be different. It is also possible that a cell can have more than one type of calcium receptor.

[0088] Comparison of calcium receptor activities and amino acid sequences from different cells indicate that distinct calcium receptor types exist. For example, calcium receptors can respond to a variety of di- and trivalent cations. The parathyroid calcium receptor responds to calcium and Gd^{3+}, while osteoclasts respond to divalent cations such as calcium but does not respond to Gd^{3+}. Thus, the parathyroid calcium receptor is pharmacologically distinct from calcium receptor on the osteoclast.

[0089] On the other hand, the nucleic acid sequences encoding calcium receptors present in parathyroid cells and C-

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

[0090] Calcium receptors, in general, have a low affinity for extracellular Ca^{2+} (apparent K_d generally greater than about 0.5 mM). Calcium receptors may include a free or bound effector mechanism as defined by Cooper, Bloom and Roth, "The Biochemical Basis of Neuropharmacology", Ch. 4, and are thus distinct from intracellular calcium receptors, e.g., calmodulin and the troponins.

[0091] Calcium receptors respond to changes in extracellular calcium levels. The exact changes depend on the particular receptor and cell line containing the receptor. For example, the in vitro effect of calcium on the calcium receptor in a parathyroid cell include the following:

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

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

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

[0092] Using techniques known in the art, the effect of calcium on other calcium receptors in different cells can be readily determined. Such effects may be similar in regard to the increase in internal calcium observed in parathyroid cells. However, the effect is expected to differ in other aspects, such as causing or inhibiting the release of a hormone other than parathyroid hormone.

II. INORGANIC ION RECEPTOR MODULATING AGENTS

[0093] Inorganic ion receptor modulating agents either evokes one or more inorganic ion receptor activities, or blocks one or more inorganic ion receptor activities caused by an extracellular inorganic ion. Calcium receptor modulating agents can mimic or block an effect of extracellular Ca^{2+} on a calcium receptor. Preferred calcium receptor modulating agents are calcimimetics and calcilytics.

[0094] Inorganic ion receptor modulating agents can be identified by screening molecules which are modeled after a molecule shown to have a particular activity (i.e., a lead molecule). Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.

[0095] Preferred inorganic ion receptor modulation agents described by the present invention have considerably low EC_{50} values.

[0096] The EC_{50} is the concentration of the molecule which evokes a half-maximal effect. The IC_{50} is the concentration of molecule which causes a half-maximal blocking effect. The EC_{50} or IC_{50} can be determined by assaying one or more of the activities of an inorganic ion at an inorganic ion receptor. Preferably, such assays are specific to a particular calcium receptor. For example, assays which measure hormones whose production or secretion is modulated by a particular inorganic ion receptor are preferred.

[0097] Increases in $[Ca^{2+}]_i$ can be detected using standard techniques such as by using fluorimetric indicators or by measuring an increase in Cl^- current in a Xenopus oocyte injected with nucleic acid coding for a calcium receptor. Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959. For example, poly(A)$^+$ mRNA can be obtained from cells expressing a calcium receptor, such as a parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, cell of the thick ascending limb of Henle's loop and/or collect-

ing duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, central nervous system cell, peripheral nervous system cell, trophoblast in the placenta, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell, and GI tract cell. Preferably, the nucleic acid is from a parathyroid cell, C-cell, or osteoclast. More preferably, the nucleic acid encodes a calcium receptor and is present on a plasmid or vector.

[0098] Preferably, the molecule is either a calcimimetic or calcilytic having an EC_{50} or IC_{50} at a calcium receptor of less than or equal to 5 mM, and even more preferably less than or equal to 1 mM, 100 nmolar, 10 nmolar, or 1 nmolar. Such lower EC_{50}'s or IC_{50}'s are advantageous since they allow lower concentrations of molecules to be used in vivo or in vitro for therapy or diagnosis. The discovery of molecules with such low EC_{50}'s and IC_{50}'s enables the design and synthesis of additional molecules having similar potency and effectiveness.

[0099] In preferred embodiments the calcium receptor modulating agent is a calcimimetic which inhibits parathyroid hormone secretion from a parathyroid cell in vitro and decreases PTH secretion in vivo; stimulates calcitonin secretion from a C-cell in vitro and elevates calcitonin levels in vivo; or blocks osteoclastic bone resorption in vitro and inhibits bone resorption in vivo.

[0100] In another preferred embodiment the calcium receptor modulating agent is a calcilytic which evokes the secretion of parathyroid hormone from parathyroid cells in vitro and elevates the level of parathyroid hormone in vivo.

[0101] Preferably, the agent selectively targets inorganic ion receptor activity, more preferably calcium receptor activity, in a particular cell. By "selectively" is meant that the molecule exerts a greater effect on inorganic ion receptor activity in one cell type than at another cell type for a given concentration of agent. Preferably, the differential effect is 10-fold or greater. Preferably, the concentration refers to blood plasma concentration and the measured effect is the production of extracellular messengers such as plasma calcitonin, parathyroid hormone or plasma calcium. For example, in a preferred embodiment, the agent selectively targets PTH secretion over calcitonin secretion.

[0102] In another preferred embodiment, the molecule has an EC_{50} or IC_{50} less than or equal to 1 mM at one or more, but not all cells chosen from the group consisting of parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, central nervous system cell, peripheral nervous system cell, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, trophoblast in the placenta, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, beta cell, fat/adipose cell, immune cell and GI tract cell.

[0103] Preferably, inorganic ion receptor modulating agents mimic or block all of the effects of extracellular ion in a cell having an inorganic ion receptor. For example, calcium receptor modulating agents preferably mimic or block all of the effects of extracellular ion in a cell having a calcium receptor. Calcimimetics need not possess all the biological activities of extracellular Ca^{2+}, but, rather, at least one such activity is mimicked. Similarly, calcilytics need not reduce or prevent all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different calcilytics do not need to bind to the same site on the calcium receptor as does extracellular Ca^{2+} to exert their effects.

A. Calcimimetics

[0104] The ability of molecules to mimic or block the activity of Ca^{2+} at calcium receptors can be determined using procedures known in the art and described by Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959. For example, calcimimetics possess one or more and preferably all of the following activities when tested on parathyroid cells in vitro:

1. The molecule causes a rapid (time to peak < 5 seconds) and transient increase in $[Ca^{2+}]_i$ that is refractory to inhibition by 1 mM La^{3+} or 1 mM Gd^{3+}. The increase in $[Ca^{2+}]_i$ persists in the absence of extracellular Ca^{2+} but is abolished by pretreatment with ionomycin (in the absence of extracellular Ca^{2+});
2. The molecule potentiates increases in $[Ca^{2+}]_i$ elicited by submaximal concentrations of extracellular Ca^{2+};
3. The increase in $[Ca^{2+}]_i$ elicited by extracellular Ca^{2+} is not inhibited by dihydropyridines;
4. The transient increase in $[Ca^{2+}]_i$ caused by the molecule is abolished by pretreatment for 10 minutes with 10 mM sodium fluoride;
5. The transient increase in $[Ca^{2+}]_i$ caused by the molecule is diminished by pretreatment with an activator of protein kinase C (PKC), such as phorbol myristate acetate (PMA), mezerein or (-)-indolactam V. The overall effect of the protein kinase C activator is to shift the concentration-response curve of the molecule to the right without affecting the maximal response;
6. The molecule causes a rapid (< 30 seconds) increase in the formation-of inositol-1,4,5-triphosphate and/or diacylglycerol;
7. The molecule inhibits dopamine- or isoproterenol-stimulated cyclic AMP formation;
8. The molecule inhibits PTH secretion;

9. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) blocks the inhibitory effect of the molecule on cyclic AMP formation but does not effect increases in $[Ca^{2+}]_i$, inositol-1,4,5-triphosphate, or diacylglycerol, nor decreases in PTH secretion;

10. The molecule elicits increases in Cl^- current in Xenopus oocytes injected with poly $(A)^+$- enriched mRNA from bovine or human parathyroid cells, but is without effect in Xenopus oocytes injected with water, or rat brain or liver mRNA; and

11. Similarly, using a cloned calcium receptor from a parathyroid cell, the molecule will elicit a response in Xenopus oocytes injected with the specific cDNA or mRNA encoding the receptor.

[0105] Different calcium activities can be measured using available techniques. Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959. Parallel definitions of molecules mimicking Ca^{2+} activity on other calcium responsive cell, preferably at a calcium receptor, are evident from the examples provided herein and Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.

[0106] Preferably, the agent as measured by the bioassays described herein, or by Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959, has one or more, more preferably all of the following activities: evokes a transient increase in internal calcium, having a duration of less that 30 seconds (preferably by mobilizing internal calcium) ; evokes a rapid increase in $[Ca^{2+}]_i$, occurring within thirty seconds; evokes a sustained increase (greater than thirty seconds) in $[Ca^{2+}]_i$ (preferably by causing an influx of external calcium); evokes an increase in inositol-1,4,5-triphosphate or diacylglycerol levels, preferably within less than 60 seconds; and inhibits dopamine- or isoproterenol-stimulated cyclic AMP formation.

[0107] The transient increase in $[Ca^{2+}]_i$ is preferably abolished by pretreatment of the cell for ten minutes with 10 mM sodium fluoride, or the transient increase is diminished by brief pretreatment (not more than ten minutes) of the cell with an activator of protein kinase C, preferably, phorbol myristate acetate (PMA), mezerein or (-)-indolactam V.

B. Calcilytics

[0108] The ability of a molecule to block the activity of external calcium can be determined using standard techniques. Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959. For example, molecules which block the effect of external calcium, when used in reference to a parathyroid cell, possess one or more, and preferably all of the following characteristics when tested on parathyroid cells in vitro:

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

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

2. The molecule blocks increases in Cl^- current in Xenopus oocytes injected with poly $(A)^+$ mRNA from bovine or human parathyroid cells elicited by extracellular Ca^{2+} or calcimimetic compounds, but not in Xenopus oocytes injected with water or liver mRNA;

3. Similarly, using a cloned calcium receptor from a parathyroid cell, the molecule will block a response in Xenopus oocytes injected with the specific cDNA, mRNA or cRNA encoding the calcium receptor, elicited by extracellular Ca^{2+} or a calcimimetic compound.

[0109] Parallel definitions of molecules blocking Ca^{2+} activity on a calcium responsive cell, preferably at a calcium receptor, are evident from the examples provided herein and Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959.

III. TREATMENT OF DISEASES OR DISORDERS

[0110] A preferred use of the compounds described by the present invention is in the treatment or prevention of different diseases or disorders by modulating inorganic ion receptor activity. The inorganic ion receptor modulating agents of the present invention can exert an affect on a inorganic ion receptor causing one or more cellular effects ultimately producing a therapeutic effect.

[0111] Different diseases and disorders can be treated by the present invention by targeting cells having an inorganic

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

[0112] Molecules that mimic the action of extracellular Ca^{2+} are beneficial in the long-term management of both primary and secondary HPT. Such molecules provide the added impetus required to suppress PTH secretion which the hypercalcemic condition alone cannot achieve and, thereby, help to relieve the hypercalcemic condition. Molecules with greater efficacy than extracellular Ca^{2+} may overcome the apparent nonsuppressible component of PTH secretion which is particularly troublesome in adenomatous tissue. Alternatively or additionally, such molecules can depress synthesis of PTH, as prolonged hypercalcemia has been shown to depress the levels of preproPTH mRNA in bovine and human adenomatous parathyroid tissue. Prolonged hypercalcemia also depresses parathyroid cell proliferation in vitro, so calcimimetics can also be effective in limiting the parathyroid cell hyperplasia characteristic of secondary HPT.

[0113] Cells other than parathyroid cells can respond directly to physiological changes in the concentration of extracellular Ca^{2+}. For example, calcitonin secretion from parafollicular cells in the thyroid (C-cells) is regulated by changes in the concentration of extracellular Ca^{2+}.

[0114] Isolated osteoclasts respond to increases in the concentration of extracellular Ca^{2+} with corresponding increases in $[Ca^{2+}]_i$ that arise partly from the mobilization of intracellular Ca^{2+}. Increases in $[Ca^{2+}]_i$ in osteoclasts are associated with the inhibition of bone resorption. Release of alkaline phosphatase from bone-forming osteoblasts is directly stimulated by calcium.

[0115] Renin secretion from juxtaglomerular cells in the kidney, like PTH secretion, is depressed by increased concentrations of extracellular Ca^{2+}. Extracellular Ca^{2+} causes the mobilization of intracellular Ca^{2+} in these cells. Other kidney cells respond to calcium as follows: elevated Ca^{2+} inhibits formation of $1,25(OH)_2$-vitamin D by proximal tubular cells, stimulates production of calcium-binding protein in distal tubular cells, and inhibits tubular reabsorption of Ca^{2+} and Mg^{2+} and the action of vasopressin on the medullary thick ascending limb of Henle's loop (MTAL), reduces vasopressin action in the cortical collecting duct cells, and affects vascular smooth muscle cells in blood vessels of the renal glomerulus.

[0116] Calcium also promotes the differentiation of intestinal goblet cells, mammary cells, and skin cells; inhibits atrial natriuretic peptide secretion from cardiac atria; reduces cAMP accumulation in platelets; alters gastrin and glucagon secretion; acts on vascular smooth muscle cells to modify cell secretion of vasoactive factors; and affects cells of the central nervous system and peripheral nervous system.

[0117] Thus, there are sufficient indications to suggest that Ca^{2+}, in addition to its ubiquitous role as an intracellular signal, also functions as an extracellular signal to regulate the responses of certain specialized cells. Molecules of this invention can be used in the treatment of diseases or disorders associated with disrupted Ca^{2+} responses in these cells.

[0118] Specific diseases and disorders which might be treated or prevented, based upon the affected cells, also include those of the central nervous system such as seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and Tourette's syndrome; diseases involving excess water reabsorption by the kidney such as syndrome of inappropriate ADH secretion (SIAH), cirrhosis, heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (e.g., aminoglycoside antibiotics); gut motility disorders such as diarrhea, and spastic colon; GI ulcer diseases; GI absorption diseases such as sarcoidosis; and autoimmune diseases and organ transplant rejection.

[0119] While inorganic ion receptor modulating agents of the present invention will typically be used in therapy for human patients, they may be used to treat similar or identical diseases or disorders in other warm-blooded animal species such as other primates, farm animals such as swine, cattle, and poultry; and sports animals and pets such as horses, dogs and cats.

IV. ADMINISTRATION

[0120] A compound of the present invention, or its pharmaceutically acceptable salt, hydrate or prodrug, can be administered to a human patient per se, or in pharmaceutical compositions where it is mixed with suitable carriers or

excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition. Administration of ionmimetics and ionlytics is discussed by Nemeth, et al., PCT/US93/01642, International Publication No. WO 94/18959.

[0121] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts, hydrates or prodrugs thereof, with other chemical components, such as physiologically acceptable carriers and excipients. The purpose of a pharmacological composition is to facilitate administration of a compound to an organism.

[0122] A "prodrug" refers to an agent which is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention wherein it is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is not beneficial, but then it is metabolically hydrolyzed to the carboxylic acid once inside the cell where water solubility is beneficial.

[0123] As used herein, an "ester" is a carboxyl group, as defined herein, wherein R" is any of the listed groups other than hydrogen.

[0124] As used herein, a "physiologically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

[0125] An "excipient" refers to an inert substance added to a pharmacological composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[0126] Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should allow the agent to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological agents or compositions injected into the blood stream should be soluble in the concentrations used. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the agent or composition from exerting its effect.

[0127] Agents can also be formulated as pharmaceutically acceptable salts (e.g., acid addition salts) and complexes thereof. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the agent without preventing it from exerting its physiological effect. Examples of useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

[0128] For systemic administration, oral administration is preferred. Alternatively, injection may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the molecules of the invention are formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, the molecules may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

[0129] Systemic administration can also be by transmucosal or transdermal means, or the molecules can be administered orally. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration may be through nasal sprays, for example, or using suppositories. For oral administration, the molecules are formulated into conventional oral administration dosage forms such as capsules, tablets, and tonics.

[0130] For topical administration, the molecules of the invention are formulated into ointments, salves, gels, or creams, as is generally known in the art.

[0131] Generally, a therapeutically effective amount is between about 1 nmole and 3 mmole of the molecule, preferably 0.1 nmole and 1 mmole depending on its EC_{50} or IC_{50} and on the age and size of the patient, and the disease or disorder associated with the patient. Generally it is an amount between about 0.1 and 50 mg/kg, preferably 0.01 and 20 mg/kg, animal to be treated.

Examples

[0132] Examples of the synthesis of the compounds of the present invention are described below. However, it is to be understood that the present invention is not restricted by the exemplified compounds.

[0133] In Examples 1 to 23, compounds represented by Fig. 1 were synthesized. The compounds of the present invention represented by the formula (1) wherein X is O were synthesized in accordance with the scheme of Fig. 2 with the use of 2-, 3- or 4-chlorophenol as the starting material. The compounds of the present invention represented by the formula (1) wherein X is S were synthesized in accordance with the scheme of Fig. 3 with the use of 2-or 4-chlorothi-

ophenol as the starting material. However, methylene chloride was used as the solvent in some cases. The compounds of the present invention represented by the formula (1) wherein Ar_1 is benzthiazole or benzoxazole were synthesized in accordance with the scheme of Fig. 4.

[0134] In Examples 24 to 36, the compounds of the present invention were synthesized in accordance with the schemes shown in Figs. 5 to 7. Example 1: Synthesis of compound 2

[0135] 500 mg (3.88 mmol) of 2-chlorophenol was dissolved in 10 ml of acetonitrile. After adding thereto 582 mg (4.28 mmol) of potassium carbonate and 1,4-dibromobutane at room temperature, the mixture was reacted while heating to 80 °C under reflux for 3 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with ethyl acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. Then the organic layer was concentrated under reduced pressure and the residue thus obtained was purified by silica gel column chromatography (50 g; hexane/acetone = 12 : 1) to thereby give 994 mg (3.88 mmol) of the compound 1 as a colorless and transparent syrup at a yield of 100 %.

[0136] Next, 994 mg (3.88 mmol) of the compound 1 obtained above was dissolved in 18 ml of acetonitrile. After adding thereto 652 mg (4.7 mmol) of potassium carbonate and 1.1 g (7.28 mmol) of (R)-3-methoxy-a-methylbenzylamine at room temperature, the mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (100 g; chloroform/methanol = 50 : 1) to thereby give 643 mg (1.93 mmol) of the compound 2 as a pale yellow and transparent syrup at a yield of 50.2%.

MS m/z : 333. 1H-NMR d: 1.34 (3H, d, J=6.7Hz), 1.60-1.73 (1H, m), 1.78-1.90 (1H, m), 2.48-2.62 (2H, m), 3.75 (3H, q, J=6.7Hz), 3.81 (3H, s), 3.98 (2H, t, J=6.7Hz), 6.77 (1H, dd, J=7.4Hz, J=2.0Hz), 6.89-6.90 (4H, m), 7.16-7.26 (2H, m), 7.34 (1H, dd, J=9.0Hz, J=2.6Hz).

Example 2: Synthesis of compound 4

[0137] The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,5-dibromopentane to thereby give the desired compound 4.

MS m/z : 347. 1H-NMR d: 1.35 (3H, d, J=6.5Hz), 1.48-1.57 (4H, m), 1.79-1.84 (2H, m), 2.44-2.55 (2H, m), 3.74 (1H, q, J=6.5Hz), 3.81 (3H, s), 4.00 (2H, t, J=6.5Hz), 6.77-6.79 (1H, m), 6.85-6.89 (4H, m), 7.16-7.26 (2H, m)

Example 3: Synthesis of compound 6 The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,6-dibromohexane to thereby give the desired compound 6.

[0138]

MS m/z : 361. 1H-NMR d: 1.35 (3H, d, J=7.0Hz), 1.34-1.39 (2H, m), 1.45-1.54 (4H, m), 1.78-1.84 (2H, m), 2.41-2.54 (2H, m), 3.73 (1H, q, J=7.0Hz), 3.81 (3H, s), 4.00 (2H, t, J= 6.5Hz), 6.77-6.78 (1H, m), 6.85-6.90 (4H, m), 7.17-7.26 (2H, m), 7.34 (1H, dd, J=8.0Hz, J= 1.0Hz).

Example 4: Synthesis of compound 8

[0139] 548 mg (4.25 mmol) of 3-chlorophenol was dissolved in 10 ml of acetonitrile. After adding thereto 652 mg (4.72 mmol) of potassium carbonate and 0.56 ml (4.69 mmol) of 1,4-dibromobutane at room temperature, the mixture was reacted while heating to 80 °C under reflux for 3 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with ethyl acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. Then the organic layer was concentrated under reduced pressure and the residue thus obtained was purified by silica gel column chromatography (50 g; hexane/acetone = 12 : 1) to thereby give 846 mg (3.31 mmol) of the compound 7 as a colorless and transparent syrup at a yield of 88.3 %.

[0140] Next, 846 mg (3.31 mmol) of the compound 7 obtained above was dissolved in 18 ml of acetonitrile. After adding thereto 523 mg (3.78 mmol) of potassium carbonate and 550 mg (3.64 mmol) of (R)-3-methoxy-a-methylbenzylamine at room temperature, the mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution

of sodium chloride. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (100 g; chloroform/methanol = 50 : 1) to thereby give 481 mg (1.46 mmol) of the compound 8 as a pale yellow and transparent syrup at a yield of 45.0%.

MS m/z :333. 1H-NMR d: 1.35 (3H, d, J=6.5Hz), 1.57-1.67 (2H, m), 1.73-1.83 (2H, m), 2.46-2.60 (2H, m), 3.74 (1H, q), 3.81 (3H, s), 3.90 (2H, t, J=6.5Hz), 6.74 (1H, dd, J=8.0Hz, J=2.5Hz),6.85-6.86 (1H, m), 7.5-7.18 (1H, dd, J=2.7Hz), 7.22-7.26 (1H, m).

Example 5: Synthesis of compound 10

[0141] The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,5-dibromopentane to thereby give the desired compound 10.

MS m/z : 347. 1H-NMR d: 1.35 (3H, d, J=6.0Hz), 1.43-1.56 (4H, m), 1.72-1.77 (2H, m), 2.43-2.56 (2H, m), 3.73 (1H, q, J=6.5Hz), 3.81 (3H, s), 3.90 (2H, t, J=7.0Hz), 6.76 (1H, dd, J=2.0Hz, J=8.5Hz), 6.70-6.79 (1H, m), 6.86-6.91 (4H, m), 7.17 (1H, dd, J=3.0Hz), 7.22-7.26 (1H, m).

Example 6: Synthesis of compound 12

[0142] The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,6-dibromohexane to thereby give the desired compound 12.

MS m/z : 361. 1H-NMR d: 1.35 (3H, d, J=6.5Hz), 1.33-1.53 (6H, m), 1.72-1.77 (2H, m), 3.73 (1H, m), 3.81 (3H, s), 3.90 (2H, t, J=6.5Hz), 6.74-6.79 (2H, m), 6.86-6.91 (4H, m), 7.17 (1H, dd, J=8.3Hz), 7.22-7.26 (1H, m).

Example 7: Synthesis of compound 14

[0143] 362 mg (2.82 mmol) of 4-chlorophenol was dissolved in 5 ml of acetonitrile. After adding thereto 429 mg (3.10 mmol) of potassium carbonate and 0.36 ml (3.01 mmol) of dibromobutane at room temperature, the mixture was reacted while heating to 80 °C under reflux for 3 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with ethyl acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. Then the organic layer was concentrated under reduced pressure and the residue thus obtained was purified by silica gel column chromatography (50 g; hexane/acetone = 12 : 1) to thereby give 414 mg (1.62 mmol) of the compound 13 as a colorless and transparent syrup at a yield of 69.4 %.

[0144] Next, 846 mg (3.31 mmol) of the compound 13 obtained above was dissolved in 18 ml of acetonitrile. After adding thereto 523 mg (3.78 mmol) of potassium carbonate and 550 mg (3.64 mmol) of (R)-3-methoxy-a-methylbenzylamine at room temperature, the mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (100 g; chloroform/methanol = 50 : 1) to thereby give 481 mg (1.46 mmol) of the compound 14 as a pale yellow and transparent syrup at a yield of 45.0 %.

MS m/z : 333. 1H-NMR d: 1.35 (3H, d, J=6.5Hz), 1.56-1.67 (2H, m), 1.73-1.83 (2H, m), 2.46-2.60 (2H, m), 3.72-3.76 (1H, q, J=6.5Hz), 3.81 (3H, s), 3.89 (2H, t, J=7.0Hz), 6.77-6.79 (3H, m), 6.88-6.90 (2H, m), 7.19-7.26 (3H, m).

Example 8: Synthesis of compound 16

[0145] The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,5-dibromopentane to thereby give the desired compound 16.

MS m/z : 347. 1H-NMR d: 1.34 (3H, d, J=6.5Hz), 1.43-1.56 (4H, m), 1.71-1.77 (2H, m), 2.42-2.55 (2H, m), 3.72 (2H, q, J=6.5Hz), 3.80 (3H, s), 3.89 (2H, t, J=6.5Hz), 6.76-6.80 (3H, m), 6.87-6.89 (2H, m), 7.19-7.26 (3H, m).

Example 9: Synthesis of compound 18

[0146] The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,6-dibromohexane to thereby give the desired compound 18.

MS m/z : 361. 1H-NMR d: 1.35 (3H, d, J=7.0Hz), 1.32-1.53 (6H, m), 1.71-1.77 (2H, m), 2.41-2.53 (2H,m) 3.73 (1H, m), 3.81 (3H, s), 3.89 (2H, t, J=7.0Hz), 6.77-6.81 (3H, m), 6.88-6.89 (3H, m), 7.19-7.26 (3H, m).

Example 10: Synthesis of compound 20

[0147] 330 mg (2.28 mmol) of 2-chlorothiophenol was dissolved in 6.5 ml of methylene chloride. After adding thereto 0.35 ml (2.51 mmol) of triethylamine and 0.23 ml (2.26 mmol) of 1,3-dibromopropane at room temperature, the mixture was reacted while heating to 45 °C under reflux for 6 hours. After the completion of the reaction, 0.30 ml (2.15 mmol) of triethylamine was dropped again into the reaction at room temperature. Then 350 mg (2.31 mmol) of (R)-3-methoxy-a-methylbenzylamine was added thereto and the resulting mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (50 g; chloroform/methanol = 65 : 1) to thereby give 102 mg (0.304 mmol) of the compound 20 as a pale yellow and transparent syrup at an overall yield of the two steps of 13.2 %.

MS m/z : 335. 1H-NMR d: 1.35 (3H, d, J=6.7Hz), 1.79-1.86 (2H, m), 2.55-2.69 (2H, m), 2.91-3.03 (2H, m), 3.74 (1H, q, J=6.7Hz), 3.81 (3H, s), 6.78 (1H, dd, J=2.5Hz, J=8.0Hz), 6.88-6.90 (2H, m), 7.07-7.11 (1H, m), 7.18-7.26 (3H, m), 7.34 (1H, dd, J=8.0Hz, J=1.2Hz).

Example 11: Synthesis of compound 22

[0148] The two steps described above were repeated but substituting the 1,3-dibromopropane with 1,4-dibromopentane to thereby give the desired compound 22.

MS m/z : 349. 1H-NMR d: 1.33 (3H, d, J=6.5Hz), 1.58-1.72 (4H, m), 2.43-2.56 (2H, m), 2.90 (2H, t, J=7.5Hz), 3.72 (1H, q, J=6.5Hz), 3.80 (3H, s), 6.76-6.78 (1H, m), 6.87-6.88 (2H, m), 7.07-7.10 (1H, m), 7.18-7.26 (3H, m), 7.35 (1H, dd, J=8.0Hz).

Example 12: Synthesis of compound 24

[0149] The two steps described above were repeated but substituting the 1,3-dibromopropane with 1,5-dibromopentane to thereby give the desired compound 24.

MS m/z : 363. 1H-NMR d: 1.34 (3H, d, J=7.0Hz), 1.42-1.55 (4H, m), 1.64-1.72 (2H, m), 2.40-2.53 (2H, m), 2.90 (2H, t, J=7.5Hz), 3.72 (1H, q, J=7.0Hz), 3.81 (3H, s), 6.77-6.79 (1H, m), 6.87-6.91 (2H, m), 7.07-7.10 (1H, m), 7.18-7.26 (3H, m), 7.35 (1H, d, J=8.0Hz).

Example 13: Synthesis of compound 26

[0150] The two steps described above were repeated but substituting the 1,3-dibromopropane with 1,6-dibromohexane to thereby give the desired compound 26.

MS m/z : 377. 1H-NMR d: 1.34 (3H, d, J=6.5Hz), 1.41-1.50 (4H, m), 1.64-1.70 (2H, m), 2.90 (2H, t, J=7.5Hz), 3.72 (1H, q, J=6.5Hz), 3.81 (3H, s), 6.77-6.79 (1H, m), 6.88-6.89 (2H, m), 7.06-7.11 (1H, m), 7.19-7.26 (3H, m), 7.35 (1H, d, J=8.0Hz).

Example 14: Synthesis of compound 28

[0151] 540 mg (3.77 mmol) of 4-chlorothiophenol was dissolved in 10 ml of methylene chloride. After adding thereto 1.60 ml (11.5 mmol) of triethylamine and 0.63 ml (4.10 mmol) of 1,3-dibromopropane at room temperature, the mixture was reacted while heating to 45 °C under reflux for 3 hours. After the completion of the reaction, the methylene chloride

was once removed under reduced pressure and the residue was dissolved in 9 ml of acetonitrile. Next, 500 mg (3.62 mmol) of potassium carbonate was added thereto at room temperature and 350 mg (2.31 mmol) of (R)-3-methoxy-a-methylbenzylamine was dropped thereinto. Then the resulting mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (75 g; chloroform/methanol = 65 : 1) to thereby give 397 mg (1.13 mmol) of the compound 28 as a pale yellow and transparent syrup at an overall yield of the two steps of 33.1 %.

MS m/z : 335. 1H-NMR d: 1.33 (3H, d, J=7.0Hz), 1.72-1.78 (2H, m), 2.50-2.55 (1H, m), 2.56-2.64 (1H, m), 2.86-2.97 (2H, m), 3.71 (1H, q, J=7.0Hz), 3.81 (3H, s), 6.77-6.79 (1H, m), 6.85-6.89 (2H, m), 7.22-7.25 (4H, m).

Example 15: Synthesis of compound 30

[0152] The two steps described above were repeated but substituting the 1,3-dibromopropane with 1,4-dibromobutane to thereby give the desired compound 30.

MS m/z : 363. 1H-NMR d: 1.35 (3H, d, J=6.7Hz), 1.39-1.49 (2H, m), 1.60 (2H, tt, J=7.5Hz), 2.39-2.44 (1H, m), 2.86 (2H, t, J=7.3Hz), 3.72 (1H, q, J=6.7Hz), 3.81 (3H, s), 6.77-6.79 (1H, m), 6.87-6.88 (2H, m), 7.20-7.26 (5H, m).

Example 16: Synthesis of compound 32

[0153] The two steps described above were repeated but substituting the 1,3-dibromopropane with 1,5-dibromopentane to thereby give the desired compound 32.

MS m/z : 377. 1H-NMR d: 1.35 (3H, d, J=6.7Hz), 1.27-1.48 (4H, m), 1.60 (2H, tt, J=7.5Hz), 2.39-2.44 (1H, m), 2.46-2.51 (1H, m), 2.85 (2H, t, J=7.3Hz), 3.72 (1H, q, J=6.7Hz), 3.81 (3H, s), 6.76-6.79 (1H, m), 6.87-6.89 (2H, m), 7.21-7.26 (5H, m).

Example 17: Synthesis of compound 34

[0154] The two steps described above were repeated but substituting the 1,3-dibromopropane with 1,6-dibromohexane to thereby give the desired compound 34.

MS m/z : 349. 1H-NMR d: 1.34 (3H, d, J=6.5Hz), 1.52-1.67 (6H, m), 2.40-2.45 (1H, m), 2.48-2.53 (1H, m), 2.86 (2H, t, J=7.0Hz), 3.71 (1H, q, J=6.5Hz), 3.80 (3H, s), 6.76-6.79 (1H, m), 6.86-6.88 (2H, m)

Example 18: Synthesis of compound 36

[0155] 440 mg (2.63 mmol) of 2-mercaptobenzothiazole was dissolved in 9 ml of methylene chloride. After adding thereto 1.1 ml (7.89 mmol) of triethylamine and 0.35 ml (2.93 mmol) of 1,4-dibromobutane at room temperature, the mixture was reacted at the same temperature for 12 hours. After the completion of the reaction, the methylene chloride was once removed under reduced pressure and the residue was dissolved in 8 ml of acetonitrile. Next, 800 mg (5.79 mmol) of potassium carbonate was added thereto at room temperature and 320 mg (2.12 mmol) of (R)-3-methoxy-a-methylbenzylamine was dropped thereinto. Then the resulting mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (70 g; chloroform/methanol = 50 : 1) to thereby give 267 mg (0.72 mmol) of the compound 36 as a pale yellow and transparent syrup at an overall yield of the two steps of 27.1 %.

MS m/z : 372 1H-NMR d: 1.34 (3H, d, J=6.5Hz), 1.61-1.68 (2H, m), 1.82-1.88 (2H, m), 2.46-2.60 (2H, m), 3.32(2H, t, J=7.5Hz), 3.73 (1H, q, J=6.5Hz), 3.80 (3H, s), 6.76-6.78 (1H, m), 6.87-6.89 (2H, m), 7.21-7.30 (2H, m), 7.38-7.42 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.84 (1H, d, J=8.0Hz).

Example 19: Synthesis of compound 38

[0156] 409 mg (2.45 mmol) of 2-mercaptobenzothiazole was dissolved in 4 ml of acetonitrile. After adding thereto 690 mg (4.99 mmol) of potassium carbonate and 0.32 ml (2.68 mmol) of 1,5-dibromopentane at room temperature, the mixture was stirred at the same temperature for 1 hour. After the completion of the reaction, 420 mg (3.04 mmol) of potassium carbonate was added thereto again and 260 mg (1.72 mmol) of (R)-3-methoxy-a-methylbenzylamine was dropped thereinto. Then the resulting mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (50 g; chloroform/methanol = 50 : 1) to thereby give 215 mg (0.57 mmol) of the compound 38 as a pale yellow and transparent syrup at an overall yield of the two steps of 45.0 %.

MS m/z: 386. 1H-NMR d: 1.33 (3H, d, J=6.5Hz), 1.44-1.56 (4H, m), 1.78-1.84 (2H, m), 2.42-2.51 (2H, m), 3.32 (2H, t, J=7.3Hz), 3.71 (1H, q, J=6.5Hz), 3.81 (3H, s), 6.76-6.78 (1H, m), 6.86-6.88 (2H, m), 7.22 (1H, dd, J=8.0Hz), 7.26-7.30 (1H, m), 7,39-7.42 (1H, m), 7.74 (1H, d, J=7.5Hz), 7.85 (1H, d, J=8.5Hz).

Example 20: Synthesis of compound 40

[0157] The two steps described above were repeated but substituting the 1,5-dibromopentane with 1,6-dibromohexane to thereby give the desired compound 40.

MS m/z : 400. 1H-NMR d: 1.34 (3H, d, J=6.5Hz), 1.43-1.50 (6H, m), 1.80 (2H, tt, J=7.5Hz), 2.40-2.52 (2H, m), 3.32 (2H, t, J=7.8Hz), 3.72 (1H, q, J=6.5Hz), 3.81 (3H, s), 6.76-6.78 (1H, m), 6.87-6.89 (2H, m), 7.22-7.30 (2H, m), 7.40 (1H, dd, J=7.5Hz), 7.74 (1H, d, J=7.5Hz), 7.85 (1H, d, J=8.0Hz).

Example 21: Synthesis of compound 42

[0158] 467 mg (3.09 mmol) of 2-mercaptobenzothiazole was dissolved in 7 ml of acetonitrile. After adding thereto 527 mg (3.81 mmol) of potassium carbonate and 0.41 ml (3.43 mmol) of 1,4-dibromobutane at room temperature, the mixture was stirred at the same temperature for 12 hours. After the completion of the reaction, 4.4 ml of acetonitrile and 420 mg (3.04 mmol) of potassium carbonate were added thereto again and 320 mg (2.12 mmol) of (R)-3-methoxy-a-methylbenzylamine was dropped thereinto. Then the resulting mixture was stirred while heating to 90 °C under reflux for 12 hours. After the completion of the reaction, the reaction mixture was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate. Then the organic layer was concentrated under reduced pressure and the residue thus obtained was purified by silica gel column chromatography (50 g; chloroform/methanol = 60 : 1) to thereby give 147 mg (0.41 mmol) of the compound 42 as a pale yellow and transparent syrup at an overall yield of the two steps of 13.4%.

MS m/z : 356. 1H-NMR d: 1.35 (3H, d, J=6.7), 1.61-1.68 (2H, m), 1.81-1.89 (2H, m), 2.46-2.59 (2H, m), 3.28 (2H, t, J=7.5Hz), 3.73 (1H, q, J=6.7Hz), 3.80 (3H, s), 6.76-6.78 (1H, m), 6.88-6.89 (2H, m), 7.21-7.28 (3H, m), 7.42 (1H, d, J=8.0Hz), 7.58 (1H, d, J=8.0Hz).

Example 22: Synthesis of compound 44

[0159] The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,5-dibromopentane to thereby give the desired compound 44.

MS m/z : 370. 1H-NMR d: 1.33 (3H, d, J=6.8Hz), 1.46-1.56 (4H, m), 1.81 (2H, m), 2.41-2.53 (2H, m), 3.29 (2H, t, J=7.3Hz), 3.72 (1H, q, J=6.8Hz), 3.81 (3H, s), 6.76-6.78 (1H, m), 6.86-6.89 (2H, m), 7.20-7.29 (1H, d, J=8.0Hz), 7.42 (1H, d, J=8.0Hz), 7.59 (1H, d, J=7.5Hz).

Example 23: Synthesis of compound 46

[0160] The two steps described above were repeated but substituting the 1,4-dibromobutane with 1,6-dibromohexane to thereby give the desired compound 46.

MS m/z : 384. 1H-NMR d: 1.34 (3H, d, J=6.5Hz), 1.32-1.62 (6H, m), 1.81 (2H, qq, J=7.5Hz), 2.40-2.52 (2H, m), 3.29 (2H, t, J=7.5Hz), 3.72 (1H, q, J=6.5Hz:), 3.81 (3H, s), 6.76-6.79 (1H, m), 6.87-6.89 (2H, m), 7.21-7.29 (3H, m), 7.43 (1H, d, J=8.0Hz), 7.59 (1H, d, J=8.0Hz).

Example 24: Synthesis of compounds 52 and 53

[0161] To a solution of 25 g (122.4 mmol) of 5-methoxygramine 47 in 500 ml of ethanol was added 21.5 g (568.3 mmol, 4.6 moleq.) of sodium tetrahydroborate and the mixture was stirred under heating for 5.5 hours. After the completion of the reaction, ammonium chloride was added to the reaction mixture. Then the mixture was stirred at room temperature, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-ethyl acetate) to thereby give 17.31 g (87.8 %) of colorless prism crystals 48.

[0162] To a solution of 17.3 g of the compound 48 (107.5 mmol) in 500 ml of absolute tetrahydrofuran was added 20 g (500 mmol, 4.6 moleq.) of 52.9 % sodium hydride and the mixture was stirred at room temperature for 1.5 hours. Then 30 g (d = 1.333, 157.4 mmol, 1.5 moleq.) of tosyl chloride was added thereto and the resulting mixture was stirred at room temperature for 6 hours. After the completion of the reaction, the reaction mixture was poured into water under ice-cooling and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-ethyl acetate) to thereby give 36.8 g (82.8 %) of colorless prism crystals 49.

[0163] 17 ml (d = 2.698, 183.1 mmol) of boron tribromide was dropped into a solution of 28.43 g (90.25 mmol) of the compound 49 in 800 ml of methylene chloride at an internal temperature of 0 to 5 °C. The mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was poured into water under ice-cooling and extracted with methylene chloride. The methylene chloride layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel: 400 g, chloroform-methanol = 1000 : 1) to thereby give 16.46 g (60.6%) of colorless prism crystals 50.

[0164] To a solution of 16.46 g (54.7 mmol) of the compound 50 in 300 ml of acetonitrile were added 11.2 ml (d = 1.333, 109.5 mmol, 2.0 moleq.) of 1,3-dibromopropane and 22 g (159.2 mmol, 2.9 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 2.5 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-acetone) to thereby give 18.34 g (79.7 %) of colorless prism crystals 51.

[0165] To a solution of 200 mg (0.48 mmol) of the compound 51 in 3 ml of acetonitrile were added 142.52 mg (0.95 mmol, 2.0 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 131.3 mg (0.95 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained yellowish brown residue was dissolved in 3 ml of ethanol and 1 ml of a 35 % aqueous solution of potassium hydroxide was added thereto. Then the mixture was stirred under heating at an external temperature of 80 °C for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 122.6 mg (93.8 %) of a colorless oil 52.

MS m/z : 338(M^+). ^{1}H-NMR d: 1.36 (3H, d, J =6.7Hz, CH_3), 1.97 (2H, dt, J =6.7, 12.8Hz, CH_2), 2.30 (3H s, CH_3), 2.67 (1H, dt, J =6.7, 11.6Hz, CH_2), 2.74 (1H, dt, J =6.7, 13.4Hz, CH_2), 3.77 (1H, q, J =6.7Hz, CH), 3.78 (3H, s, OCH_3), 4.07 (2H, m, CH_2), 6.78 (1H, dd, J =1.8, 7.9Hz, C_6-H), 6.82 (1H, dd, J =1.8, 7.9Hz, C_6'-H), 6.90 (2H, d, J =1.8Hz, C_2-H), 6.91 (1H, d, J =7.9Hz, C_4-H), 6.94 (1H, s, C_2'-H), 6.99 (1H, d, J =1.8Hz, C_4'-H), 7.21 (1H, d, J =7.9Hz, C_7'-H), 7.23 (1H, t, J =7.9Hz, C_5-H), 7.81 (1H, s, NH).

[0166] To a solution of 200 mg (0.48 mmol) of the compound 51 in 3 ml of acetonitrile were added 162.7 mg (0.95 mmol, 2.0 moleq.) of (R)-1-(1-naphthyl)ethylamine and 131.3 mg (0.95 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was

washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained yellowish brown residue was dissolved in 1 ml of ethanol and 1 ml of a 35 % aqueous solution of potassium hydroxide was added thereto. Then the mixture was stirred under heating at an external temperature of 80 °C for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 122.6 mg (93.8 %) of a colorless oil 53.

MS m/z : 358(M^+). ^{1}H-NMR d: 1.53 (3H, d, J =6.7Hz, CH_3), 2.03 (2H, dt, J =6.7, 12.8Hz, CH_2), 2.30 (3H, s, CH_3), 2.83 (2H, dt, J =6.7, 12.8Hz, CH_2), 4.12 (2H, dt, J =3.1, 9.2Hz, CH_2), 4.68 (1H, q, J =6.7Hz, CH), 6.83 (1H, dd, J =1.8, 9.2Hz, C_2-H), 6.94 (1H, s, C_2'-H), 7.01 (1H, d, J =1.8Hz, C_4'-H), 7.21 (1H, d, J =7.9Hz, C_4-H), 7.48 (1H, t, J =7.9Hz, C_3-H), 7.49 (1H, t, J =7.9Hz, C_6-H), 7.50 (1H, t, J =7.9Hz, C_7-H), 7.68 (1H, d, J =7.9Hz, C_5-H), 7.75 (1H, d, J =7.9Hz, C_8-H), 7.82 (1H, s, NH), 7.88 (1H, dd, J =1.8, 7.9Hz, C_6'-H), 8.21 (1H, d, J =7.9Hz, C_7'-H).

Example 25: Synthesis of compound 56

[0167] To a solution of 500 mg (2.74 mmol) of 9-hydroxyfluorene 54 in 5 ml of toluene were added 0.273 ml (d = 1.537, 3.02 mmol, 1.1 moleq.) of 3-bromo-1-propanol and 5.1 mg (0.027 mmol, 0.01 moleq.) of p-toluenesulfonic acid and the resulting mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 723.4 mg (87.0 %) of a colorless oil 55.

[0168] To a solution of 200 mg (0.66 mmol) of the compound 55 in 3 ml of acetonitrile were added 148.5 mg (0.99 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 136.8 mg (0.99 mmol, 1.5 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 216.6 mg (88.0 %) of a colorless oil 56.

MS m/z : 373(M^+). ^{1}H-NMR d: 1.30 (3H, d, J =6.7Hz, CH_3), 1.67 (2H, dt, J =6.7, 13.4Hz, CH_2), 2.49 (1H, dt, J =6.7, 14.0Hz, CH_2), 2.56 (1H, dt, J =6.7, 11.6Hz, CH_2), 3.21 (2H, t, J =6.7Hz, CH_2), 3.69 (1H, q, J =6.7Hz, CH), 3.78 (3H, s, OCH_3), 5.59 (1H, s, CH), 6.76 (1H, dd, J =1.8, 7.9Hz, C_6-H), 6.85 (1H, d, J =1.8Hz, C_2-H), 6.87 (1H, d, J =7.9Hz, C_4-H), 7.21 (1H, t, J =7.9Hz C_5-H), 7.28 (2H, t, J =7.9Hz, C_3', C_6'-H), 7.37 (2H, t, J =7.9Hz, C_2', C_7'-H), 7.53 (1H, d, J =7.9Hz, C_4'-H), 7.55 (1H, d, J =7.9Hz, C_5'-H), 7.65 (2H, d, J =7.9Hz, C_1', C_8'-H), 7.81 (1H, s, NH).

Example 26: Synthesis of compound 59

[0169] To a solution of 200 mg (1.1 mmol) of 2-hydroxyfluorene 57 in 3 ml of acetonitrile were added 0.22 ml (d = 1.333, 2.2 mmol, 2.0 moleq.) of 1,3-dibromopropane and 182.0 mg (1.32 mmol, 1.2 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 202.4 mg (73.3 %) of a colorless prism crystals 58.

^{1}H-NMR d: 2.35 (2H, dt, J =6.1, 12.2Hz, CH_2), 3.64 (2H, t, J =6.1Hz, CH_2), 3.86 (2H, s, C_9-H_2), 4.17 (2H, t, J =6.1Hz, CH_2), 6.93 (1H, dd, J =1.8, 7.3Hz, C_2-H), 7.11 (1H, d, J =1.8Hz, C_4-H), 7.23 (1H, t, J =7.3Hz, C_6-H), 7.34 (1H, t, J =7.3Hz, C_7-H), 7.50 (1H, d, J =7.3Hz, C_1-H), 7.67 (1H, d, J =6.7Hz, C_8-H), 7.69 (1H, t, J =6.7Hz, C_5-H).

[0170] To a solution of 100 mg (0.33 mmol) of the compound 58 in 3 ml of acetonitrile were added 49.5 mg (0.33 mmol, 1.0 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 54.7 mg (0.40 mmol, 1.2 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica

gel, ethyl acetate-n-hexane) to thereby give 216.6 mg (88.0 %) of a colorless oil 59.

MS m/z : 373(M^+). ^{1}H-NMR d: 1.36 (3H, d, J =6.7Hz CH_3), 1.96 (2H, m, CH_2), 2.65 (1H, dt, J =6.7, 11.6Hz, CH_2), 2.73 (1H, dt, J =6.7, 12.2Hz, CH_2), 3.77 (1H, q, J =6.7Hz, CH), 3.78 (3H, s, OCH_3), 3.85 (2H, s, CH_2), 4.07 (2H, q, J =5.5Hz, C_9-H_2), 6.77 (1H, dd, J =1.8, 7.3Hz, C_6-H), 6.89 (1H, d, J =1.2Hz, C_2-H), 6.90 (1H, d, J =7.3Hz, C_4-H), 6.90 (1H, d, J =7.3Hz, C_2'-H), 7.06 (1H, s, C_4'-H), 7.22 (1H, t, J =7.3Hz, C_5-H), 7.22 (1H, t, J =7.3Hz, C_6'-H), 7.33 (1H, t, J =7.3Hz, C_7'-H), 7.49 (1H, d, J =7.3Hz, C_1'-H), 7.65 (1H, d, J =7.3Hz, C_8'-H), 7.68 (1H, d, J =7.3Hz, C_5'-H).

Example 27: Synthesis of compound 62

[0171] To a solution of 500 mg (3.89 mmol) of o-chlorophenol 60 in 3 ml of acetonitrile were added 0.39 ml (d = 1.989, 3.89 mmol, 1.0 moleq.) of 1,3-dibromopropane and 591.2 mg (4.28 mmol, 1.1 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 824.0 mg (84.9 %) of a colorless oil 61.

[0172] To a solution of 200 mg (0.66 mmol) of the compound 61 in 3 ml of acetonitrile were added 148.5 mg (0.99 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 136.8 mg (0.99 mmol, 1.5 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 222.6 mg (87.1 %) of a colorless oil 62.

MS m/z : 319(M^+). ^{1}H-NMR d: 1.37 (3H, d, J =6.7Hz, CH_3), 1.99 (2H, dt, J =6.7, 12.2Hz, CH_2), 2.67 (1H, dt, J =6.7, 13.4Hz, CH_2), 2.75 (1H, dt, J =6.7, 11.6Hz, CH_2), 3.75-3.79 (1H, m, CH), 3.78 (3H, s, OCH_3), 4.09 (2H, dt, J=1.8, 6.1Hz, CH_2), 6.77 (1H, dd, J =1.8, 7.3Hz, C_6-H), 6.89 (1H, t, J =7.9Hz, C_4-H), 6.90 (1H, d, J =1.8Hz, C_2-H), 6.90 (1H, d, J =7.9Hz, C_4-H), 6.90 (1H, d, J =7.9Hz, C_3'-H), 7.20 (1H, dt, J =1.8, 7.3Hz, C_5'-H), 7.22 (1H, t, J =7.9Hz, C_5-H), 7.4 (1H, dd, J =1.8, 7.9Hz, C_6'-H).

Example 28: Synthesis of compound 65

[0173] To a solution of 500 mg (3.89 mmol) of m-chlorophenol 63 in 3 ml of acetonitrile were added 0.39 ml (d = 1.989, 3.89 mmol, 1.0 moleq.) of 1,3-dibromopropane and 591.2 mg (4.28 mmol, 1.1 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 884.2 mg (91.1 %) of a colorless oil 64.

[0174] To a solution of 200 mg (0.66 mmol) of the compound 64 in 3 ml of acetonitrile were added 148.5 mg (0.99 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 136.8 mg (0.99 mmol, 1.5 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 229.3 mg (89.7 %) of a colorless oil 65.

MS m/z : 319(M^+). ^{1}H-NMR d: 1.35 (3H, d, J =6.7Hz, CH_3), 1.88-1.96 (2H, m, CH_2), 2.61 (1H, dt, J =6.7, 11.6Hz, CH_2), 2.70 (1H, dt, J =6.7, 11.6Hz, CH_2), 3.75 (1H, q, J =6.7Hz, CH), 3.80 (3H, s, OCH_3), 3.96-4.04 (2H, m, CH_2), 6.75 (1H, d, J =7.9Hz, C_6-H), 6.78 (1H, d, J =7.9Hz, C_6-H), 6.80 (1H, s), 6.88-6.92 (3H, m), 7.17 (1H, t, J =7.9Hz, C_5'-H), 7.23 (1H, t, J =7.9Hz, C_5-H).

Example 29: Synthesis of compound 68

[0175] To a solution of 500 mg (3.89 mmol) of p-chlorophenol 66 in 3 ml of acetonitrile were added 0.39 ml (d = 1.989, 3.89 mmol, 1.0 moleq.) of 1,3-dibromopropane and 591.2 mg (4.28 mmol, 1.1 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the

reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 876.5 mg (90.3 %) of a colorless oil 67.

[0176] To a solution of 200 mg (0.66 mmol) of the compound 67 in 3 ml of acetonitrile were added 148.5 mg (0.99 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 136.8 mg (0.99 mmol, 1.5 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 293.1 mg (87.2 %) of a colorless oil 68.

MS m/z : 319 (M^+). ^{1}H-NMR (90MHz) d: 1.35 (3H, d, J =6.4Hz, CH_3), 1.91 (2H, dt, J =6.4, 12.7Hz, CH_2), 2.67 (2H, dt, J =2.4, 6.4Hz, CH_2), 3.75 (1H, q, J =6.4Hz, CH), 3.79 (3H, s, OCH_3), 3.98 (2H, t, J =6.4Hz, CH_2), 6.70-6.91 (5H, m), 7.14 (3H, m).

Example 30: Synthesis of compound 71

[0177] To a solution of 500 mg (2.71 mmol) of 3-hydroxybenzofuran 69 in 5 ml of acetonitrile were added 0.55 ml (d = 1.989, 5.43 mmol, 2.0 moleq.) of 1,3-dibromopropane and 750.1 mg (5.43 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 804.3 mg (77.0 %) of colorless prism crystals 70.

[0178] To a solution of 800 mg (2.62 mmol) of the compound 70 in 5 ml of acetonitrile were added 590.2 mg (3.93 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 543.7 mg (3.93 mmol, 1.5 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 880.8 mg (89.5 %) of a colorless oil 71.

MS m/z : 375(M^+). ^{1}H-NMR d: 1.38 (3H, d, J =6.7Hz, CH_3), 2.01 (2H, m, CH_2), 2.70 (1H, dt, J =6.7, 14.0Hz, CH_2), 2.77 (1H, dt, J =6.7, 13.4Hz, CH_2), 3.80 (1H, q, J =6.7Hz, CH), 3.80 (3H, s, OCH_3), 4.10-4.17 (2H, m, CH_2), 6.79 (1H, dd, J =1.8, 7.3Hz, C_6-H), 6.91 (1H, d, J =1.8Hz, C_2-H), 6.92 (1H, d, J =7.3Hz, C_4-H), 7.02 (1H, dd, J =2.5, 8.6Hz, C_3'-H), 7.24 (1H, t, J =7.3Hz, C_5-H), 7.33 (1H, t, J =7.3Hz, C_6'-H), 7.41 (1H, d, J =2.5Hz, C_1'-H), 7.45 (1H, dt, J =1.2, 7.3Hz, C_7'-H), 7.46 (1H, d, J =7.3Hz, C_5'-H), 7.55 (1H, d, J =8.6Hz, C_4'-H), 7.91 (1H, d, J =7.3Hz, C_8'-H).

Example 31: Synthesis of compound 74

[0179] To a solution of 300.0 mg (2.16 mmol) of 2-naphthol 72 in 3 ml of absolute tetrahydrofuran were added 300 ml (d = 1.537, 2.16 mmol, 1.0 moleq.) of 3-bromo-1-propanol and 622.7 mg (2.37 mmol, 1.1 moleq.) of triphenylphosphine. Then a solution of 0.41 ml (d = 1.106, 2.37 mmol, 1.1 moleq.) of DEAD in 3 ml of absolute tetrahydrofuran was added thereto and the resulting mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 551.8 mg (100 %) of a colorless oil 73.

[0180] To a solution of 200 mg (0.75 mmol) of the compound 73 in 5 ml of acetonitrile were added 169.8 mg (1.13 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 156.5 mg (1.13 mmol, 1.5 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 230.8 mg (91.3 %) of a colorless oil 74.

MS m/z : 335 (M^+). ^{1}H-NMR d: 1.41 (3H, d, J =6.7Hz, CH_3), 2.13 (2H, dt, J =6.7, 12.8Hz, CH_2), 2.73 (1H, dt, J =6.7,

11.6Hz, CH_2), 2.85 (1H, dt, J =6.7, 11.6Hz, CH_2), 3.79 (3H, s, OCH_3), 3.83 (1H, q, J =6.7Hz, CH), 4.23 (2H, dt, J =1.2, 6.1 Hz, CH_2), 6.80 (1H,dd, J =2.4, 7.9Hz, C_6-H), 6.83 (1H, d, J =7.3Hz, C_2'-H), 6.92 (1H, d, J =2.4Hz, C_2-H), 6.93 (1H, d, J =7.9Hz, C_4-H), 7.24 (1H, t, J =7.9Hz, C_5-H), 7.39 (1H, t, J =7.9Hz, C_6'-H), 7.45 (1H, d, J =7.9Hz, C_4'-H), 7.48 (1H, dd, J =1.2, 7.9Hz, C_3'-H), 7.52 (1H, dt, J =1.2, 7.9Hz, C_7'-H), 7.83 (1H, d, J =7.9Hz, C_5'-H), 8.22 (1H, d, J =7.9Hz, C_8'-H).

Example 32: Synthesis of compound 77

[0181] To a solution of 300 mg (1.87 mmol) of 2-naphthalenethiol 75 in 5 ml of methylene chloride were added 0.23 ml (d = 1.989, 2.25 mmol, 1.2 moleq.) of 1,3-dibromopropane and 0.31 mg (d = 0.726, 2.25 mmol, 1.2 moleq.) of triethylamine and the resulting mixture was stirred under heating at an external temperature of 40 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with a 5 % aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 241.3 mg (45.9 %) of a colorless oil 76.

[0182] To a solution of 241 mg (0.86 mmol) of the compound 76 in 5 ml of acetonitrile were added 193.0 mg (1.29 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 177.8 mg (1.29 mmol, 1.5 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 209.8 mg (69.7 %) of a colorless oil 77.

MS m/z : 351(M^+). ^{1}H-NMR d: 1.38 (3H, d, J =6.7Hz, CH_3), 2.01 (2H, dt, J =6.7Hz, CH_2), 2.73 (2H, dt, J =6.7, 25.0Hz, CH_2), 3.80 (1H, q, J =6.7Hz, CH), 3.80 (3H, s, OCH_3), 4.13 (2H, m, CH_2), 6.79 (1H, dd, J =1.8, 7.3Hz, C_6-H), 6.91 (1H, d, J =1.2Hz, C_2-H), 6.92 (1H, d, J =7.3Hz, C_4-H), 7.02 (1H, dd, J =2.5, 7.3Hz, C_3'-H), 7.24 (1H, t, J =7.3Hz, C_5-H), 7.33 (1H, t, J =7.3Hz, C_6'-H), 7.41 (1H, d, J =2.5Hz, C_1'-H), 7.45 (1H, dt, J =1.2, 7.3Hz, C_7'-H), 7.46 (1H, d, J =7.3Hz, C_4'-H), 7.55 (1H, d, J =7.3Hz, C_5'-H), 7.91 (1H, d, J =7.3Hz, C_8'-H).

Example 33: Synthesis of compound 80

[0183] To a solution of 500 mg (3.76 mmol) of 5-hydroxyindole 78 in 5 ml of acetonitrile were added 833.9 mg (d = 1.989, 4.13 mmol, 1.1 moleq.) of 1,3-dibromopropane and 570.9 mg (4.13 mmol, 1.1 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 586 mg (61.4 %) of a colorless oil 79.

^{1}H-NMR d: 2.33 (2H, dt, J =6.1, 12.2Hz, CH_2), 3.63 (2H, t, J =6.1Hz, CH_2), 4.13 (2H, t, J =6.1Hz, CH_2), 6.47 (1H, t, J =2.4Hz:, C_3-H), 6.85 (1H, dd, J =2.4, 8.5Hz, C_6-H), 7.12 (1H, d, J =2.4Hz, C_4-H), 7.17 (1H, t, J =2.4Hz, C_2-H), 7.26 (1H,d, J =8.5Hz, C_7-H), 8.03 (1H, s, NH).

[0184] To a solution of 200 mg (0.79 mmol) of the compound 79 in 3 ml of acetonitrile were added 118.1 g (0.79 mmol, 1.5 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 130.6 mg (0.94 mmol, 1.2 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 40 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 265.1 mg (82.8 %) of a colorless oil 80.

MS m/z : 324(M^+). ^{1}H-NMR d: 1.38 (3H, d, J =6.7Hz, CH_3), 2.01 (2H, dt, J =6.7, 12.8Hz, CH_2), 2.67 (1H, dt, J =6.7, 11.6Hz, CH_2), 2.74 (1H, dt, J =6.7, 13.4Hz, CH_2), 3.78 (1H, q, J =6.7Hz, CH), 3.81 (3H, s, OCH_3), 4.02-4.09 (2H, m, CH_2), 6.47 (1H, t, J =3.1Hz, C_3'-H), 6.78 (1H, dd, J =3.1, 7.9Hz, C_6-H), 6.83 (1H, dd, J =2.4, 8.5Hz, C_6'-H), 6.90 (1H, d, J =3.1Hz, C_2-H), 6.91 (1H, d, J =7.9Hz, C_4-H), 7.09 (1H, d, J =2.4Hz, C_4'-H), 7.18 (1H, t, J =3.1Hz, C_2'-H), 7.23 (1H, t, J =7.9Hz, C_5-H), 7.27 (1H, d, J =8.5Hz, C_7'-H), 8.07 (1H, s, NH).

Example 34: Synthesis of compound 83

[0185] To a solution of 400 mg (2.35 mmol) of 4-phenylphenol 81 in 5 ml of acetonitrile were added 0.48 ml (d = 1.989, 4.7 mmol, 2.0 moleq.) of 1,3-dibromopropane and 389.7 mg (2.82 mmol, 1.2 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 564.9 mg (82.5 %) of colorless prism crystals 82.

[0186] To a solution of 300 mg (1.03 mmol) of the compound 82 in 4 ml of acetonitrile were added 309.3 mg (2.06 mmol, 2.0 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 284.9 mg (2.06 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an external temperature of 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 311.9 mg (83.8 %) of colorless prism crystals 83.

MS m/z : 361 (M^+). ^{1}H-NMR d: 1.36 (3H, d, J =6.7Hz CH_3), 1.93-2.01 (2H, m, CH_2), 2.65 (1H, dt, J =6.7, 11.6Hz, CH_2), 2.73 (1H, dt, J =6.7, 11.6Hz, CH_2), 3.77 (1H, q, J =6.7Hz, CH), 3.80 (3H, s, OCH_3), 4.02-4.10 (2H, m, CH_2), 6.79 (1H,dd, J =1.8, 7.3Hz, C_6-H), 6.90 (1H, d, J =1.8Hz, C_2-H), 6.91 (1H, d, J =7.3Hz, C_4-H), 6.95 (2H, dt, J =2.4, 9.2Hz, C_3'-H), 7.24 (1H, t, J =7.3Hz, C_5-H), 7.30 (1H, t, J =7.3Hz, C_4"-H), 7.42 (2H, t, J =7.3Hz, C_3", $_5$"-H), 7.51 (2H, dt, J =2.4, 9.2Hz, C_2", $_6$"-H), 7.55 (2H, dd, J =1.2, 7.3Hz, C_2',$_6$'-H).

Example 35: Synthesis of compound 88

[0187] To a solution of 600 mg (4.0 mmol) of (R)-3-methoxy-a-methylbenzylamine 84 in 5 ml of methylene chloride were added 662.4 mg (d = 1.176, 4.4 mmol, 1.1 moleq.) of ethylmalonyl chloride and 0.66 ml (d = 0.726, 4.8 mmol, 1.2 moleq.) of triethylamine and the resulting mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride layer was washed with a 5 % aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 790.0 mg (98.4 %) of colorless prism crystals 85.

^{1}H-NMR d: 1.21 (3H, t, J =6.7Hz, CH_2CH_3), 1.42 (3H, d, J =6.7Hz, CH_3), 3.23 (2H, d, J =4.3Hz, CH_2), 3.73 (3H, s, OCH_3), 4.12 (2H, q, J =6.7Hz, CH_2CH_3), 5.04 (1H, dt, J =6.7, 14.0Hz, CH), 6.72 (1H, dd, J =1.8, 7.9Hz, C_6-H), 6.79 (1H, d, J =1.8Hz, C_2-H), 6.83 (1H, d, J =7.9Hz, C_4-H), 7.18 (1H, t, J =7.9Hz, C_5-H), 7.36 (1H, s, NH).

[0188] To a solution of 897.6 mg (3.39 mmol) of the compound 85 in 5 ml of ethanol was added 2 ml of a 10 % aqueous solution of sodium hydroxide and the resulting mixture was stirred under heating at an external temperature of 80 °C for 1 hour. After the completion of the reaction, the reaction mixture was concentrated and acidified with a 5 % aqueous solution of hydrochloric acid. Then the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with a 5 % aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 790.0 mg (98.4 %) of colorless prism crystals 86.

^{1}H-NMR d: 1.47 (3H, d, J =6.7Hz, CH_3), 3.27 (2H, d, J =9.2Hz, CH_2), 3.77 (3H, s, OCH_3), 5.05 (1H, dt, J =6.7, 14.0Hz, CH), 6.78 (1H, dd, J =2.4, 7.9Hz, C_6-H), 6.83 (1H, d, J =2.4Hz, C_2-H), 6.86 (1H, d, J =7.9Hz, C_4-H), 7.23 (1H, t, J =7.9Hz, C_5-H), 7.47 (1H, d, J =7.9Hz, NH).

[0189] To a solution of 400 mg (1.68 mmol) of the compound 86 in 5 ml of dimethylformamide were added 278.5 mg (1.86 mmol, 1.1 moleq.) of (R)-3-methoxy-a-methylbenzylamine and 389.5 mg (2.02 mmol, 1.2 moleq.) of WSC×HCl and the resulting mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 615.4 mg (98.5 %) of colorless prism crystals 87.

MS m/z : 370(M^+). ^{1}H-NMR d: 1.42 (6H, d, J =6.7Hz, CH_3), 3.15 (2H, s, CH_2), 3.75 (6H, s, OCH_3), 5.04 (2H, dt, J =7.9, 14.7Hz, CH), 6.77 (2H, dd, J =2.4, 7.9Hz, $C_{6,6'}$-H), 6.80 (2H, d, J =2.4Hz, $C_{2,2'}$-H), 6.83 (2H, d, J =7.9Hz, $C_{4,4'}$-H), 7.20 (2H, t, J =7.9Hz, $C_{5,5'}$-H), 7.47 (2H, s, NH).

[0190] To a solution of 100 mg (0.270 mmol) of the compound 87 in 5 ml of absolute tetrahydrofuran was added 0.59 ml (0.59 mmol, 1.2 moleq.) of a 1 mol solution of boron trihydride in tetrahydrofuran. The resulting mixture was heated to room temperature and then stirred for 3 hours. After the completion of the reaction, the reaction mixture was poured into water, acidified with a 5 % aqueous solution of hydrochloric acid and then extracted with ethyl acetate. The hydrochloric acid layer was made alkaline by adding a 5 % aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 76.3 mg (82.6 %) of a colorless oil 88.

MS m/z : 342(M^+). ^{1}H-NMR d: 1.43 (6H, d, J =6.7Hz, CH_3), 1.62 (2H, dt, J =6.7, 13.4Hz, CH_2), 2.46 (2H, dt, J =6.7, 13.4Hz, CH_2), 2.54 (2H, dt, J =6.7, 11.6Hz, CH_2), 3.70 (2H, q, J =6.7Hz, CH), 3.80 (6H, s, OCH_3), 6.77 (2H, dd, J =2.4, 7.3Hz, $C_{6,6'}$-H), 6.86 (2H, d, J =2.4Hz, $C_{2,2'}$-H), 6.87 (2H, d, J =7.3Hz, $C_{4,4'}$-H), 7.23 (2H, t, J =7.3Hz, $C_{5,5'}$-H).

Example 36: Synthesis of compound 93

[0191] To a solution of 600 mg (3.5 mmol) of (R)-1-(1-naphthyl)ethylamine 89 in 5 ml of methylene chloride were added 580.3 mg (d = 1.176, 3.85 mmol, 1.1 moleq.) of ethylmalonyl chloride and 0.59 ml (d = 0.726, 4.2 mmol, 1.2 moleq.) of triethylamine and the resulting mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride layer was washed with a 5 % aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 662.9 mg (66.5 %) of colorless prism crystals 90.

^{1}H-NMR d: 1.16 (3H, t, J =7.3Hz, CH_2CH_3), 1.60 (3H, d, J =7.3Hz, CH_3), 3.24 (2H, dd, J =17.7, 26.3Hz, CH_2), 4.07 (2H, q, J =7.3Hz, CH_2CH_3), 5.89 (1H, dt, J =7.3, 14.6Hz, CH), 7.35 (1H, d, J =7.9Hz, NH), 7.38 (1H, t, J =7.9Hz, C_3-H), 7.44 (1H, t, J =12.2Hz, C_6-H), 7.45 (1H, d, J =7.9Hz, C_2-H), 7.46 (1H, t, J =12.2Hz, C_7-H), 7.72 (1H, d, J =7.9Hz, C_4-H), 7.79 (1H, d, J =7.9Hz, C_5-H), 8.03 (1H, d, J =7.9Hz, C_8-H).

[0192] To a solution of 662.5 mg (2.32 mmol) of the compound 90 in 5 ml of ethanol was added 2 ml of a 10 % aqueous solution of sodium hydroxide. The resulting mixture was stirred under heating at an external temperature of 80 °C for 1 hour. After the completion of the reaction, the reaction mixture was concentrated, acidified with a 5 % aqueous solution of hydrochloric acid. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with a 5 % aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 596.0 mg (99.8 %) of colorless prism crystals 91.

^{1}H-NMR d: 1.66 (3H, d, J =6.7Hz, CH_3), 3.20 (2H, dd, J =18.3, 29.9Hz, CH_2), 5.91 (1H, dt, J =6.7, 14.7Hz, CH), 6.99 (1H, d, J =7.3Hz, NH), 7.43 (1H, t, J =7.9Hz, C_3-H), 7.48 (1H, t, J =7.9Hz, C_6-H), 7.49 (1H, d, J =7.9Hz, C_2-H), 7.53 (1H, dt, J =1.2, 7.9Hz, C_7-H), 7.77 (1H, d, J =7.9Hz, C_4-H), 7.83 (1H, d, J =7.9Hz, C_5-H), 8.00 (1H, d, J =7.9Hz, C_8-H).

[0193] To a solution of 400 mg (1.56 mmol) of the compound 91 in 5 ml of dimethylformamide were added 293.2 mg (1.71 mmol, 1.1 moleq.) of (R)-1-(1-naphthyl)ethylamine and 359.2 mg (1.87 mmol, 1.2 moleq.) of WSC×HCl and the resulting mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 615.1 mg (96.4 %) of colorless prism crystals 92.

[0194] To a solution of 100 mg (0.24 mmol) of the compound 92 in 5 ml of absolute tetrahydrofuran was added 0.54 ml (0.54 mmol, 2.2 moleq.) of a 1 mol solution of boron trihydride in tetrahydrofuran. The resulting mixture was heated to room temperature and then stirred for 3 hours. After the completion of the reaction, the reaction mixture was poured into water, acidified with a 5 % aqueous solution of hydrochloric acid and then extracted with ethyl acetate. The hydro-

chloric acid layer was made alkaline by adding a 5 % aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 82.0 mg (88.0 %) of a colorless oil 93.

MS m/z : 382(M^+). ^{1}H-NMR d: 1.47 (6H, d, J =6.7Hz, CH_3), 1.72 (2H, dt, J =6.7, 13.4Hz, CH_2), 2.62 (2H, dt, J =6.7, 13.4Hz, CH_2), 2.68 (2H, dt, J =6.7, 11.6Hz, CH_2), 4.60 (2H, q, J =6.7, CH), 7.45 (2H, t, J =7.9Hz, $C_{3,3'}$-H), 7.48 (2H, dt, J =1.8, 7.9Hz, $C_{6,6'}$-H), 7.50 (2H, t, J =7.9Hz, $C_{7,7'}$-H), 7.60 (2H, d, J =7.9Hz, $C_{2,2'}$-H), 7.74 (2H, d, J =7.9Hz, $C_{4,4'}$-H), 7.87 (2H, dd, J =1.8, 7.9Hz, $C_{5,5'}$-H), 8.16 (2H, d, J =7.9Hz, $C_{8,8'}$-H).

Example 37: Synthesis of compound 103

Compound 102:

[0195] To a solution of 6-hydroxyflavone 101 (300 mg, 1.26 mmol) in acetonitrile (5 ml) were added 1,3-dibromopropane (0.26 ml, d = 1.989, 2.52 mmol, 2.0 mol eq.) and potassium carbonate (208.8 mg, 1.51 mmol, 1.2 mol eq.) and the resulting mixture was stirred under heating at an outer temperature of 60 °C for 4 hours.

[0196] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 361.8 mg (80.0 %) of the compound 102 as colorless prisms.

MS m/z : 375(M^+). ^{1}H-NMR δ: 2.34-2.39(2H, m, CH_2), 3.62(2H, t, J=6.7Hz, CH_2), 4.22(2H, t, J=6.7Hz, CH_2), 6.82(1H, s, Ar-H), 7.29(1H, dd, J=3.1, 9.2Hz, Ar-H), 7.51 (4H, m, Ar-H), 7.61(1H, d, J=3.1Hz, Ar-H), 7.92(1H, dd, J=1.8, 7.9Hz, Ar-H), 7.19(1H, dd, J=3.1, 9.2Hz, Ar-H), 7.44-7.53(7H, m, Ar-H), 7.57(1H, d, J=3.1Hz, Ar-H), 7.68(1H, d, J=7.3Hz, Ar-H), 7.74(1H, d, J=7.9Hz, Ar-H), 7.86(H, d, J=7.9Hz, Ar-H), 7.91 -7.93(2H, m, Ar-H), 8.19(1H, d, J=8.5Hz, Ar-H).

Compound 103:

[0197] To a solution of the above compound 102 (125.8 mg, 0.38 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred under heating at an outer temperature of 40 °C for 6 hours.

[0198] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 67.1 mg (89.5 %) of the compound 103 as a colorless oil.

MS m/z : 449(M^+). ^{1}H-NMR δ: 1.55(3H, d, J=6.7Hz, CH_3), 2.04(2H, t, J=6.1Hz, CH_2), 2.07(1H, s, NH), 2.82(2H, m, CH_2), 4.15(1H, t, J=6.1Hz, CH_2), 4.71 (1H, q, J=6.7Hz, CH), 6.82(1H, s, Ar-H), 7.19(1H, dd, J=3.1, 9.2Hz, Ar-H), 7.44-7.53(7H, m, Ar-H), 7.57(1H, d, J=3.1Hz, Ar-H), 7.68(1H, d, J=7.3Hz, Ar-H), 7.74(1H, d, J=7.9Hz, Ar-H), 7.86(1H, d, J=7.9Hz, Ar-H), 7.91-7.93(2H, m, Ar-H), 8.19(1H, d, J=8.5Hz Ar-H).

Example 38: Synthesis of compound 106

Compound 105:

[0199] To a solution of 9-hydroxyfluorene 104 (500 mg, 2.74 mmol) in toluene (5 ml) were added 3-bromo-1-propanol (0.273 ml, d = 1.537, 3.02 mmol, 1.1 mol eq.) and p-toluenesulfonic acid hydrate (5.1 mg, 0.027 mmol, 0.01 mol eq.) and the resulting mixture was stirred at room temperature for 1 hour.

[0200] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, n-hexane/ethyl acetate] to thereby give the compound 105 (723.4 mg, 87.0 %) as a colorless oil.

Compound 106:

[0201] To a solution of the above compound 105 (106.2 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (48.4 mg, 0.35 mmol, 1.2 mol eq.) and the resulting mixture was stirred under heating at an outer temperature of 60 °C for 6 hours.

[0202] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 33.7 mg (76.1 %) of the compound 106 as a colorless oil.

MS m/z: 393(M^+). ^{1}H-NMR δ: 1.47(3H, d, J=6.1Hz, CH_3), 1.70-1.76(2H, m, CH_2), 2.60-2.71 (2H, m, CH_2), 3.26(2H, t, J=6.1Hz, CH_2), 4.61(1H, q, J=6.7Hz, CH), 5.59(1H, s, CH), 7.26(1H, t, J=7.3Hz, Ar-H), 7.28(1H, t, J=7.3Hz, Ar-H), 7.37(1H, d, J=7.3Hz, Ar-H), 7.38(1H, t, J=7.3Hz, Ar-H), 7.46(1H, t, J=7.3Hz, Ar-H), 7.48(1H, t, J=7.3Hz, Ar-H), 7.49(1H, t, J=7.9Hz, Ar-H), 7.53(1H, d, J=7.3Hz, Ar-H), 7.54(1H, d, J=7.3Hz, Ar-H), 7.63(1H, d, J=6.7Hz, Ar-H), 7.66(2H, d, J=7.9Hz, Ar-H), 7.75(1H, d, J=8.5Hz, Ar-H), 7.88(1H, d, J=7.9Hz, Ar-H), 8.20(1H, d, J=8.5Hz, Ar-H).

Example 39: Synthesis of compound 109

Compound 108:

[0203] To a solution of 2-hydroxybenzofuran 107 (500 mg, 2.71 mmol) in acetonitrile (5 ml) were added 1,3-dibromopropane (0.55 ml, d = 1.989, 5.43 mmol, 2.0 mol eq.) and potassium carbonate (750.1 mg, 5.43 mmol, 2.0 mol eq.) and the resulting mixture was stirred at an outer temperature of 60 °C for 4 hours.

[0204] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 804.3 mg (77.0 %) of the compound 108 as colorless prisms.

Compound 109:

[0205] To a solution of the above compound 108 (106.9 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred under heating at an outer temperature of 60 °C for 6 hours.

[0206] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 67.2 mg (58.3 %) of the compound 109 as a colorless oil.

MS m/z: 395(M^+). ^{1}H-NMR δ: 1.53(3H, d, J=6.7Hz, CH_3), 2.02-2.07(2H, m, CH_2), 2.78-2.89(2H, m, CH_2), 4.13-4.16(2H, m, CH_2), 4.69(1H, q, J=6.7Hz, CH), 7.00(1H, dd, J=2.4, 8.6Hz, Ar-H), 7.33(1H, t, J=7.3Hz, Ar-H), 7.38(1H, d, J=2.4Hz, Ar-H), 7.44-7.51(6H, m, Ar-H), 7.67(1H, d, J=7.3Hz, Ar-H), 7.75(1H, d, J=7.9Hz, Ar-H), 7.87(1H, dd, J=2.4, 9.7H, Ar-H), 7.89(1H, d, J=7.9Hz, Ar-H), 8.22(1H, d, J=8.6Hz, Ar-H).

Example 40: Synthesis of compound 112

Compound 111:

[0207] To a solution of 5-hydroxyindole 110 (500 mg, 3.76 mmol) in acetonitrile (5 ml) were added 1,3-dibromopropane (833.9 mg, d = 1.989, 4.13 mmol, 1.1 mol eq.) and potassium carbonate (570.9 mg, 4.13 mmol, 1.1 mol eq.) and the resulting mixture was stirred under heating at an outer temperature of 60 °C for 4 hours.

[0208] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 586 mg (61.4 %) of the compound 111 as a colorless oil.

^{1}H-NMR δ: 1.70(3H, d, J=6.7Hz, C$\underline{H}_2$), 3.63(2H, t, J=6.7Hz, C$\underline{H}_2$), 4.13(2H, t, J=6.7Hz, C$\underline{H}_2$), 6.47(1H, t, J=2.4Hz, Ar-$\underline{H}$), 6.85(1H, dd, J=2.4, 9.2Hz, Ar-$\underline{H}$), 7.12(1H, d, J=2.4Hz, Ar-$\underline{H}$), 7.17(1H, t, J=2.4Hz, Ar-$\underline{H}$), 7.26(1H, d, J=8.5Hz, Ar-$\underline{H}$), 8.03(1H, s, N$\underline{H}$).

Compound 112:

[0209] To a solution of the above compound 111 (65.3 mg, 0.26 mmol, 1.5 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-naphthyl)ethylamine (29.3 mg, 0.17 mmol) and potassium carbonate (35.5 mg, 0.26 mmol, 1.5 mol eq.) and the resulting mixture was stirred under heating at an outer temperature of 60 °C for 6 hours.

[0210] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 36.5 mg (62.0 %) of the compound 112 as a colorless oil.

MS m/z: 344(M$^+$). ^{1}H-NMR δ: 1.52(3H, d, J=6.1Hz, C$\underline{H}_3$), 1.99-2.04(2H, m, C$\underline{H}_2$), 2.76-2.86(2H, m, C$\underline{H}_2$), 4.05-4.12(2H, m, C$\underline{H}_2$), 4.67(1H, q, J=6.1Hz, CH), 6.47(1H, s, Ar-$\underline{H}$), 6.83(1H, dd, J=2.4, 8.6Hz, Ar-$\underline{H}$), 7.09(1H, d, J=2.4Hz, Ar-$\underline{H}$), 7.17(1H, t, J=2.4Hz, Ar-$\underline{H}$), 7.26(1H, d, J=9.2Hz, Ar-$\underline{H}$), 7.44-7.50(3H, m, Ar-$\underline{H}$), 7.67(1H, d, J=7.3Hz, Ar-$\underline{H}$), 7.74(1H, d, J=8.5Hz, Ar-$\underline{H}$), 7.87(1H, dd, J=2.4, 6.7Hz, Ar-$\underline{H}$), 8.10(1H, s, N$\underline{H}$), 8.20(1H, d, J=7.9Hz, Ar-$\underline{H}$).

Example 41: Synthesis of compound 117

Compound 114:

[0211] To a solution of (R)-(+)-1-(1-naphthyl)ethylamine (600 mg, 3.5 mmol) in dichloromethane (5 ml) were added ethylmalonyl chloride 113 (580.3 mg, 3.85 mmol, 1.1 mol eq.) and triethylamine (0.59 ml, d = 0.726, 3.85 mmol, 1.1 mol eq.) and the resulting mixture was stirred at room temperature for 2 hours.

[0212] After the completion of the reaction, the reaction mixture was poured into water and extracted with dichloromethane. The dichloromethane layer was washed successively with a 5 % aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 662.9 mg (66.5 %) of the compound 114 as colorless prisms.

^{1}H-NMR δ: 1.16(3H, t, J=7.3Hz, $CH_2C\underline{H}_3$), 1.60(3H, d, J=7.3Hz, C$\underline{H}_3$), 3.24(2H, dd, J=17.7, 26.3Hz, C$\underline{H}_2$), 4.07(2H, q, J=7.3Hz, C$\underline{H}_2CH_3$), 5.89(1H, dt, J=7.3, 14.6Hz, CH), 7.35(1H, d, J=7.9Hz, N$\underline{H}$), 7.38(1H, t, J=7.9Hz), Ar-$\underline{H}$, 7.44(1H, t, J=12.2Hz, Ar-$\underline{H}$), 7.46(1H, t, J=12.2Hz, Ar-$\underline{H}$), 7.72(1H, d, J=7.9Hz, Ar-$\underline{H}$), 7.79(1H, d, J=7.9Hz, Ar-$\underline{H}$) 8.03(1H, d, J=7.9Hz, Ar-$\underline{H}$).

Compound 115:

[0213] To a solution of the above compound 114 (662.5 mg, 2.32 mmol) in ethanol (5 ml) was added a 10 % aqueous solution of sodium hydroxide (1 ml) and the resulting mixture was stirred under heating at an outer temperature of 80 °C for 1 hour.

[0214] After the completion of the reaction, the reaction mixture was concentrated, acidified with a 5 % aqueous solution of hydrochloric acid, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed successively with a 5 % aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 659.5 mg of the compound 115 as colorless prisms.

^{1}H-NMR δ: 1.66(3H, d, J=6.7Hz, C$\underline{H}_3$), 3.20(2H, dd, J=18.3, 29.9Hz, C$\underline{H}_2$), 5.91(1H, dt, J=6.7, 14.7Hz, CH), 6.99(1H, d, J=7.3Hz, N$\underline{H}$), 7.43(1H, t, J=7.9Hz, Ar-$\underline{H}$), 7.48(1H, d, J=7.9Hz, Ar-$\underline{H}$), 7.53(1H, dt, J=1.2, 6.7Hz, Ar-$\underline{H}$), 7.77(1H, d, J=8.5Hz, Ar-$\underline{H}$), 7.83(1H, d, J=7.9Hz, Ar-$\underline{H}$), 8.00(1H, d, J=8.5Hz, Ar-$\underline{H}$).

Compound 116:

[0215] To a solution of the above compound 115 (50 mg, 0.19 mmol) in N,N-dimethylformamide (3 ml) were added

(R)-(+)-1-(1-naphthyl)ethylamine (45.0 mg, 0.21 mmol, 1.1 mol eq.) and WSC • HCl (44.9 mg, 0.23 mmol, 1.2 mol eq.) and the resulting mixture was stirred at room temperature for 1 hour.

[0216] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 61.6 mg (70.5 %) of the compound 116 as colorless prisms.

^{1}H-NMR δ: 1.43(3H, d, J=6.7Hz, $CH_2C\underline{H}_3$), 1.72(3H, d, J=6.7Hz, $C\underline{H}_3$), 3.38(2H, d, J=2.5Hz, $C\underline{H}_2$), 4.36(2H, q, J=6.7Hz, $C\underline{H}_2CH_3$), 5.32-6.01(1H, m, CH), 6.88(1H, d, J=9.2Hz, Ar-H), 7.21(1H, t, J=6.7Hz, Ar-H), 7.33(1H, d, J=8.6Hz, Ar-H), 7.40(1H, d, J=7.9Hz, Ar-H), 7.44-7.56(5H, m, Ar-H), 7.80(1H, d, J=7.9Hz, Ar-H), 7.88(1H, d, J=9.2Hz, Ar-H), 8.06(1H, d, J=7.9Hz, Ar-H), 8.11(1H, d, J=8.5Hz, Ar-H), 8.29(1H, d, J=1.8Hz, Ar-H).

Compound 117:

[0217] To a solution of the above compound 116 (50 mg, 0.11 mol) in tetrahydrofuran (3 ml) was added a 1 M solution of borane-tetrahydrofuran (0.24 ml, 0.24 mmol, 2.2 mol eq.) under ice-cooling. Then the temperature was elevated to room temperature and the mixture was stirred for 6 hours.

[0218] After the completion of the reaction, water was poured into the reaction mixture. Then the mixture was acidified with a 5 % aqueous solution of hydrochloric acid and extracted with ethyl acetate. The layer of the 5 % aqueous solution of hydrochloric acid was made alkaline by adding a 5 % aqueous solution of sodium hydroxide and then extracted with ethyl acetate. After washing with water and a saturated aqueous solution of sodium chloride and drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 18.0 mg (88.0 %) of the compound 117 as a colorless oil.

MS m/z: 421 (M^+). ^{1}H-NMR δ: 1.38(3H, d, J=7.3Hz, $CH_2C\underline{H}_3$), 1.56(3H, d, J=6.7Hz, $C\underline{H}_3$), 1.90(2H, m, $C\underline{H}_2$), 2.75(1H, m, $C\underline{H}_2$), 2.81(2H, m, $C\underline{H}_2$), 3.29(2H, t, J=6.7Hz, $C\underline{H}_2$), 4.29(2H, q, J=7.3Hz, $C\underline{H}_2CH_3$), 4.79(1H, q, J=6.1Hz, CH), 6.81(1H, dd, J=1.8, 8.6Hz, Ar-H), 7.13(1H, t, J=7.3Hz, Ar-H), 7.20(1H, d, J=8.6Hz, Ar-H), 7.27(1H, d, J=1.8Hz, Ar-H), 7.32(1H, d, J=7.9Hz, Ar-H), 7.39(1H, t, J=7.3Hz, Ar-H), 7.46(3H, m, Ar-H), 7.65(1H, d, J=10.4Hz, Ar-H), 7.75(1H, d, J=8.6Hz, Ar-H), 7.86(1H, dd, J=2.4, 6.7Hz, Ar-H), 7.98(1H, d, J=7.3Hz, Ar-H), 8.16(1H, d, J=8.6Hz, Ar-H).

Example 42: Synthesis of compound 123

Compound 119:

[0219] 2-Methoxycarbonylthiophenol 118 (9.7 g) was dissolved in N,N-dimethylformamide (200 ml) and sodium hydride (60 %) (2.7 g) was added thereto at 0 °C. When foaming was ceased, (±)-2-tert-butoxycarbonylamino-1-methanesulfonyloxy-2-phenylethane (20.0 g) was added thereto and the resulting mixture was stirred at room temperature for 12 hours.

[0220] After the completion of the reaction, ammonium chloride was added thereto in excess and the reaction mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 16.0 g of the compound 119.

Compound 120:

[0221] The above compound 119 (1.9 g) was dissolved in diphenyl ether and p-toluenesulfonic acid hydrate (100 mg) was added thereto. The resulting mixture was heated at 250 to 260 °C for 40 minutes.

[0222] After cooling by allowing to stand, it was purified by column chromatography and eluted with ethyl acetate/n-hexane to thereby give 700 mg of the compound 120.

Compound 121:

[0223] The above compound 120 (150 g) was dissolved in tetrahydrofuran and lithium aluminum hydride (310 mg) was added thereto. The resulting mixture was then heated under reflux for 5 hours.

[0224] After the completion of the reaction, sodium sulfate decahydrate was added in excess thereto and the mixture was filtered through celite. The filtrate was concentrated and thus 330 mg of the compound 121 was obtained.

Compound 122:

[0225] The above compound 121 (3.0 g) and triethylamine (1.5 g) were dissolved in tetrahydrofuran and acryloyl chloride (1.2 g) was added thereto under ice-cooling. After stirring the mixture at room temperature for 30 minutes, a saturated aqueous solution of sodium hydrogen carbonate was added thereto followed by extraction with chloroform. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 1.5 g of the compound 122.

Compound 123:

[0226] The above compound 122 (150 mg, 0.51 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (104.5 mg, 0.61 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (3 ml) and then allowed to stand at room temperature for 1 week.

[0227] After the completion of the reaction, the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform/ methanol] to thereby give 167.4 mg (70.7 %) of the compound 123 as a colorless oil.

MS m/z: 466(M^+). ^{1}H-NMR δ: 1.46(3H, q, J=6.7Hz, CH_3), 2.33-2.36(1H, m, CH_2), 2.79-2.93(3H, m, CH_2), 3.25-3.38(1H, m, CH_2), 3.57-3.65(1H, m, CH_2), 4.41-4.45(1H, m, CH_2), 4.56-4.65(2H, m, CH_2), 6.30-6.34(1H, m, CH), 7.07-7.17(3H, m, Ar-H), 7.27-7.51(9H, m, Ar-H), 7.63(1H, t, J=4.9Hz, Ar-H), 7.73(1H, t, J=8.5Hz, Ar-H), 7.84-7.87(1H, m, Ar-H), 8.11-8.19(1H, m, Ar-H).

Example 43: Synthesis of K-2003

[0228] 4-Bromophenol (520 mg, 3.01 mmol) was dissolved in acetonitrile (11 ml) and then potassium carbonate (1.243 g, 8.99 mmol) and 1,3-dibromopropane (0.37 ml, 3.64 mmol) were successively added thereto at room temperature. The resulting mixture was stirred under heat-reflux at 95 °C for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (800 mg, 5.79 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (450 mg, 2.98 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 18 hours.

[0229] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 100 : 1) to thereby give 364 mg (1.00 mmol) of the compound K-2003 as a pale yellow syrup at a yield of 33 %.

500MHz NMR 7.22(1H, dd, J=8.3Hz, J=8.3Hz), 7.34(2H, dd, J=8.3Hz, J=8.3Hz), 6.87-6.88(1H, m), 6.87(1H, s), 6.76-6.78(1H, m), 6.74(2H, dd, J=8.3Hz, J=2.0Hz), 3.93-4.00(2H, m), 3.79(3H, s), 3.74(1H, q, J=6.5Hz), 2.58-2.71(2H, m), 1.88-1.95(2H, m), 1.53(1H, m), 1.34(3H, d, J=6.5Hz), m/z=363, 365.

Example 44: Synthesis of K-2004

[0230] 4-Bromophenol (570 mg, 3.29 mmol) was dissolved in acetonitrile (11 ml) and then potassium carbonate (1.08 g, 7.81 mmol) and 1,4-dibromobutane (0.44 ml, 3.68 mmol) were successively added thereto at room temperature. The resulting mixture was stirred under heat-reflux at 95 °C for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (455 mg, 3.29 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (400 mg, 2.64 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 18 hours.

[0231] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 100:1) to thereby give 422 mg (1.11 mmol) of the compound K-2004 as a pale yellow syrup at a yield of 43 %.

500MHz NMR 7.34(2H, d, J=9.0Hz), 7.23(1H, dd, J=8.3Hz, J=8.3Hz), 6.77-6.88(3H, m), 6.73(2H, d, J=6.5Hz), 3.86(2H, t, J=6.5Hz), 3.80(3H, s), 3.72(1H, q, J=7.0Hz), 2.46-2.59(2H, m), 1.73-1.83(2H, m), 1.56-1.67(2H, m),

1.51(1H, s), 1.34(3H, d, J=7.0Hz), m/z=377, 379.

Example 45: Synthesis of K-2005

[0232] 4-Bromophenol (710 mg, 4.10 mmol) was dissolved in acetonitrile (11 ml) and then potassium carbonate (710 mg, 5.14 mmol) and 1,5-dibromopentane (0.44 ml, 4.55 mmol) were successively added thereto at room temperature. The resulting mixture was stirred under heat-reflux at 95 °C for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (455 mg, 3.29 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (370 mg, 2.45 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 24 hours.

[0233] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 100: 1) to thereby give 295 mg (0.75 mmol) of the compound K-2005 as a pale yellow syrup at a yield of 31 %.

500MHz NMR 7.34(2H, d, J=7.0Hz), 7.23(1H, dd, J=8.5Hz, J=8.5Hz), 6.87-6.89(2H, m), 6.77(1H, dd, J=8.5Hz, J=1.5Hz), 6.74(2H, d, J=8.5Hz), 3.88(2H, t, J=6.3Hz), 3.80(3H, m), 3.72(1H, q, J=6.5Hz), 2.36-2.55(4H, m), 1.55-1.77(2H, m), 1.43-1.57(2H, m), 1.34(3H, d, J=6.5Hz), m/z=391, 393.

Example 46: Synthesis of K-2006

[0234] 4-Bromophenol (500 mg, 2.89 mmol) was dissolved in acetonitrile (10 ml) and then potassium carbonate (540 mg, 3.90 mmol) and 1,6-dibromohexane (0.49 ml, 3.18 mmol) were successively added thereto at room temperature. The resulting mixture was stirred under heat-reflux at 95 °C for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (400 mg, 2.89 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (270 mg, 1.79 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 24 hours.

[0235] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform: methanol = 100 : 1) to thereby give 364 mg (0.896 mmol) of the compound K-2006 as a pale yellow syrup at a yield of 50 %.

500MHz NMR 7.34(2H, d, J=8.0Hz), 7.23(1H, dd, J=8.0Hz, J=8.0Hz), 6.88-6.89(1H, m), 6.88(1H, s), 6.78(1H, dd, J=8.0Hz, J=3.0Hz), 6.75(2H, d, J=8.0Hz), 3.88(2H, t, J=6.3Hz), 3.81(3H, s), 3.73(1H, q, J=7.0Hz), 2.41-2.53(2H, m), 1.71-1.77(2H, m), 1.35-1.52(7H, m), 1.34(3H, d, J=7.0Hz), m/z=405, 407.

Example 47: Synthesis of K-2007

[0236] 4-Bromophenol (490 mg, 2.83 mmol) was dissolved in acetonitrile (10 ml) and then potassium carbonate (495 mg, 3.58 mmol) and 1,7-dibromoheptane (0.53 ml, 3.10 mmol) were successively added thereto at room temperature. The resulting mixture was stirred under heat-reflux at 95 °C for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (400 mg, 2.89 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (300 mg, 1.98 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 24 hours.

[0237] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform: methanol = 100 : 1) to thereby give 150 mg (0.36 mmol) of the compound K-2007 as a pale yellow syrup at a yield of 18 %.

500MHz NMR 7.34(2H, d, J=8.5Hz), 7.24(1H, dd, J=7.8Hz, J=7.8Hz), 6.90-6.93(2H, m), 6.79(1H, dd, J=7.8Hz, J=1.8Hz), 6.75(2H, d, J=8.5Hz), 3.88(2H, t, J=6.3Hz), 3.82(3H, s), 3.79-3.80(1H, m), 2.43-2.54(2H, m), 1.70-1.84(2H, m), 1.20-1.56(9H, m), 1.41(3H, d, J=6.5Hz), m/z=419, 421.

Example 48: Synthesis of K-2010

[0238] 3-Trifluoromethylthiophenol (615 mg, 3.45 mmol) was dissolved in acetonitrile (12 ml) and then potassium carbonate (467 mg, 3.38 mmol) and 1,4-dibromobutane (0.46 ml, 3.85 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (210 mg, 1.52 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (360 mg, 2.38 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 18 hours.

[0239] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 180 mg (0.47 mmol) of the compound K-2010 as a pale yellow syrup at a yield of 20%.

500MHz NMR 7.51 (1H, s), 7.35-7.44(3H, m), 7.23(1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.88(2H, m), 6.76-6.78(1H, m), 3.80(3H, s), 3.71(1H, q, J=6.5Hz), 2.93(2H, t, J=7.5Hz), 2.50-2.55(1H, m), 2.42-2.47(1H, m), 1.55-1.71 (4H, m), 1.45(1H, s), 1.33(3H, d, J=6.5Hz), m/z=383.

Example 49: Synthesis of K-2011

[0240] 3-Trifluoromethylthiophenol (600 mg, 3.37 mmol) was dissolved in acetonitrile (12 ml) and then potassium carbonate (540 mg, 3.96 mmol) and 1,5-dibromopentane (0.50 ml, 3.67 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (240 mg, 1.74 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (300 mg, 1.98 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 18 hours.

[0241] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 220 mg (0.55 mmol) of the compound K-2011 as a pale yellow syrup at a yield of 28 %.

500MHz NMR 7.51(1H, s), 7.45-7.44(1H, m), 7.35-7.40(2H, m), 7.23(1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.88(2H, m), 6.76-6.79(1H, m), 3.81 (3H, s), 3.71(1H, q, J=6.5Hz), 2.93(2H, t, J=7.3Hz), 2.47-2.52(1H, m), 2.40-2.45(1H, m), 1.61-1.67(2H, m), 1.41-1.52(5H, m), 1.34(3H, d, J=6.5Hz), m/z=397.

Example 50: Synthesis of K-2012

[0242] 3-Trifluoromethylthiophenol (515 mg, 2.89 mmol) was dissolved in acetonitrile (10 ml) and then potassium carbonate (440 mg, 3.18 mmol) and 1,6-dibromohexane (0.45 ml, 2.93 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (270 mg, 1.95 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (260 mg, 1.72 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 24 hours.

[0243] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 272 mg (0.66 mmol) of the compound K-2012 as a pale yellow syrup at a yield of 38 %.

500MHz NMR 7.51(1H, s), 7.43-7.45(1H, m), 7.35-7.40(2H, m), 7.23(1H, dd, J=7.5Hz, J=7.5Hz), 6.87-6.89(2H, m), 6.76-6.79(1H, m), 3.81(3H, s), 3.71(1H, q, J=6.5Hz), 2.93(2H, t, J=7.5Hz), 2.46-2.51(1H, m), 2.40-2.44(1H, m), 1.61-1.67(2H, m), 1.38-1.50(7H, m), 1.34(3H, d, J=6.5Hz), m/z=411.

Example 51: Synthesis of K-2015

[0244] 2-Bromobenzenethiol (445 mg, 2.35 mmol) was dissolved in acetonitrile (10 ml) and then potassium carbonate (420 mg, 3.04 mmol) and 1-bromo-2-chloroethane (0.22 ml, 2.64 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (315 mg, 2.28 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.65 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 120 hours.

[0245] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 207 mg (0.57 mmol) of the compound K-2015 as a pale yellow syrup at a yield of 34 %.

500MHz NMR 7.53(1H, d, J=8.0Hz), 7.18-7.26(4H, m), 6.87-6.88(2H, m), 6.78-6.81(1H, m), 3.81(3H, s), 3.04(2H, t, J=7.0Hz), 3.76(1H, q, J=6.5Hz), 2.67-2.81(2H, m), 1.73(1H, s), 1.35(3H, d, J=6.5Hz), m/z=365, 367.

Example 52: Synthesis of K-2016

[0246] 2-Bromobenzenethiol (517 mg, 2.73 mmol) was dissolved in acetonitrile (10 ml) and then potassium carbonate (475 mg, 3.44 mmol) and 1,3-dibromopropane (0.31 ml, 3.05 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (352 mg, 2.76 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.65 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 12 hours.

[0247] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 249 mg (0.66 mmol) of the compound K-2016 as a pale yellow syrup at a yield of 40 %.

500MHz NMR 7.52(1H, d, J=7.5Hz), 7.22-7.26(3H, m), 7.00(1H, ddd, J=7.5Hz, J=7.5Hz, J=2.0Hz), 6.88(1H, d, J=7.5Hz), 6.87(1H, s), 6.77(1H, dd, J=7.5Hz, J=2.0Hz), 3.81(3H, s), 3.73(1H, q, J=7.0Hz), 2.90-3.02(2H, m), 2.55-2.69(2H, m), 1.80-1.86(2H, m), 1.46(1H, s), 1.34(3H, d, J=7.0Hz), m/z=379, 3.81.

Example 53: Synthesis of K-2017

[0248] 2-Bromobenzenethiol (505 mg, 2.67 mmol) was dissolved in acetonitrile (10 ml) and then potassium carbonate (445 mg, 3.22 mmol) and 1,4-dibromobutane (0.35 ml, 2.93 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (330 mg, 2.39 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.65 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 12 hours.

[0249] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 311 mg (0.79 mmol) of the compound K-2017 as a pale yellow syrup at a yield of 48 %.

500MHz NMR 7.52(1H, d, J=8.0Hz), 7.19-7.25(3H, m), 7.00(1H, ddd, J=8.0Hz, 8.0Hz, J=2.0Hz), 6.87-6.88(2H, m), 6.78(1H, dd, J=2.0Hz, J=8.0Hz), 3.80(3H, s), 3.72(1H, q, J=6.5Hz), 2.90(2H, t, J=7.5Hz), 2.43-2.56(2H, m), 1.68-1.73(2H, m), 1.68-1.73(2H, m), 1.58-1.67(2H, m), 1.47(1H, s), 1.34(3H, d, J=6.5Hz), m/z=393, 395.

Example 54: Synthesis of K-2018

[0250] 2-Bromobenzenethiol (445 mg, 2.35 mmol) was dissolved in acetonitrile (10 ml) and then potassium carbonate (407 mg, 2.95 mmol) and 1,5-dibromopentane (0.31 ml, 2.60 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 4 hours. After confirming the completion of the reaction by TLC, potassium carbonate (330 mg, 2.39 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (220 mg, 1.46 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 12 hours.

[0251] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 307 mg (0.75 mmol) of the compound K-2018 as a pale yellow syrup at a yield of 52 %.

500MHz NMR 7.52(1H, d, J=6.5Hz), 7.18-7.25(3H, m), 6.99(1H, dd, J=7.5Hz, J=7.5Hz), 6.87-6.89(2H, m), 6.78(1H, dd, J=7.5Hz, J=2.0Hz), 3.81(3H, s), 3.72(1H, q, J=6.5Hz), 2.90(2H, q, J=7.5Hz), 2.41-2.51(2H, m), 1.65-1.69(2H, m), 1.44-1.53(5H, m), 1.34(3H, d, J=6.5Hz), m/z=409.

Example 55: Synthesis of K-2027 (N-{5-[(4-chlorophenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0252] 4-Chlorobenzenethiol (550 mg, 3.80 mmol) was dissolved in acetonitrile (6.0 ml) and then potassium carbonate (520 mg, 3.76 mmol) and 1,5-dibromopentane (0.52 ml, 3.82 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (241 mg, 1.74 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.31 ml, 1.92 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 95 °C for additional 12 hours.

[0253] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 288 mg (0.75 mmol) of the compound K-2027 as a pale yellow syrup at a yield of 40 %.

500MHz NMR 8.17(1H, d, J=8.0Hz), 7.87(1H, d, J=7.5Hz), 7.74(1H, d, J=9.0Hz), 7.63(1H, d, J=9.0Hz), 7.63(1H, d, J=7.5Hz), 7.45-7.52(3H, m), 7.19-7.23(4H, m), 4.61(1H, q, J=6.5Hz), 2.85(2H, t, J=7.2Hz), 2.50-2.61(2H, m), 1.41-1.63(7H, m), 1.48(3H, d, J=6.5Hz), m/z=383.

Example 56: Synthesis of K-2030

[0254] 3-Chlorophenol (420 mg, 3.27 mmol) was dissolved in acetonitrile (9.0 ml) and then potassium carbonate (1.19 g, 8.61 mmol) and 1-bromo-2-chloroethane (0.41 ml, 4.93 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at 70 °C for 24 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.70 g, 12.3 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.45 ml, 2.79 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 120 hours.

[0255] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 321 mg (0.99 mmol) of the compound K-2030 as a pale yellow syrup at a yield of 35 %.

500MHz NMR 8.21(1H, d, J=8.5Hz), 7.87(1H, d, J=7.5Hz), 7.75(1H, d, J=8.0Hz), 7.69(1H, d, J=8.0Hz), 7.46-7.53(3H, m), 7.18(1H, dd, J=8.0Hz), 6.89-3.93(2H, m), 6.76-6.78(1H, dd, J=1.5Hz, J=8.0Hz), 4.71(1H, q, J=6.5Hz), 4.04(2H, t, J=5.3Hz), 2.90-3.00(2H, m), 1.78(1H, s), 1.53(3H, d, J=6.5Hz), m/z=325.

Example 57: Synthesis of K-2033

[0256] 4-Nitrobenzenethiol (470 mg, 3.03 mmol) was dissolved in acetonitrile (7.0 ml) and then potassium carbonate (450 mg, 3.26 mmol) and 1,4-dibromobutane (0.36 ml, 3.01 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (250 mg, 1.81 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.65 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 12 hours.

[0257] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform: methanol = 150 : 1) to thereby give 206 mg (0.57 mmol) of the compound K-2033 as a yellow syrup at a yield of 35 %.

500MHz NMR 8.11(2H, d, J=9.0Hz), 7.29(2H, d, J=9.0Hz), 7.24(1H, dd, J=8.0Hz, J=8.0Hz), 6.88(1H, d, J=8.0Hz), 6.87(1H, s), 6.79(1H, dd, J=8.0Hz, J=2.5Hz), 3.81(3H, s), 3.72(1H, q, J=6.5Hz), 2.99(2H, t, J=7.5Hz), 2.44-2.60(2H, m), 1.71-1.76(2H, m), 1.60-1.66(3H, m), 1.35(3H, d, J=6.5Hz), m/z=360.

Example 58: Synthesis of K-2034

[0258] 4-Nitrobenzenethiol (520 mg, 3.35 mmol) was dissolved in acetonitrile (7.0 ml) and then potassium carbonate (492 mg, 3.56 mmol) and 1,5-dibromopentane (0.46 ml, 3.38 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (300 mg, 2.17 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (300 mg, 1.98 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 12 hours.

[0259] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 102 mg (0.27 mmol) of the compound K-2034 as a yellow syrup at a yield of 14 %.

500MHz NMR 8.11(2H, d, J=9.5Hz), 7.28(2H, d, J=9.5Hz), 7.24(1H, dd, J=7.8Hz, J=7.8Hz), 6.87-6.89(2H, m), 6.77-6.79(1H, m), 3.81(3H, s), 3.72(1H, q, J=6.5Hz), 2.99(2H, q, J=7.5Hz), 2.49-2.52(1H, m), 2.41 -2.45(1H, m), 1.67-1.72(2H, m), 1.45-1.53(5H, m), 1.35(3H, d, J=6.5Hz), m/z=374.

Example 59: Synthesis of K-2035

[0260] 4-Nitrobenzenethiol (460 mg, 2.96 mmol) was dissolved in acetonitrile (7.0 ml) and then potassium carbonate (432 mg, 3.13 mmol) and 1,6-dibromohexane (0.46 ml, 2.99 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (120 mg, 0.86 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (230 mg, 1.52 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 12 hours.

[0261] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 133 mg (0.342 mmol) of the compound K-2035 as a yellow syrup at a yield of 23 %.

500MHz NMR 8.12(2H, d, J=9.0Hz), 7.29(2H, d, J=9.0Hz), 7.24(1H, dd, J=8.0Hz), 6.88(1H, d, J=8.0Hz), 6.88(1H, s), 6.77-6.79(1H, m), 3.81(3H, s), 3.73(1 H, q, J=6.5Hz), 2.99(2H, t, J=7.5Hz), 2.40-2.53(2H, m), 1.67-1.73(2H, m), 1.41-1.50(5H, m), 1.25-1.36(2H, m), 1.35(3H, d, J=6.5Hz), m/z=388.

Example 60: Synthesis of K-2040

[0262] 4-Fluorobenzenethiol (520 mg, 4.06 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (864 mg, 6.26 mmol) and 1,4-dibromobutane (0.49 ml, 4.12 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 10 hours. After confirming the completion of the reaction by TLC, potassium carbonate (320 mg, 2.32 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (310 mg, 2.05 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 12 hours.

[0263] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 170 mg (0.51 mmol) of the compound K-2040 as a pale yellow syrup at a yield of 25 %.

500MHz NMR 7.28-7.32(2H, m), 7.23(1H, dd, J=8.3Hz, J=8.3Hz), 6.95-6.70(2H, m), 6.86-6.87(2H, m), 6.76-6.79(1H, m), 3.80(3H, s), 3.71(1H, q, J=6.5Hz), 2.83(2H, dd, J=7.0Hz, J=7.0Hz), 2.47-2.52(1H, m), 2.39-2.44(1H, m), 1.52-1.64(5H, m), 1.33(3H, d, J=6.5Hz), m/z=333.

Example 61: Synthesis of K-2041

[0264] 4-Fluorobenzenethiol (590 mg, 4.61 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (340 mg, 2.46 mmol) and 1,5-dibromopentane (0.63 ml, 4.62 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (340 mg, 2.46 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (350 mg, 2.31 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 12 hours.

[0265] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 245 mg (0.71 mmol) of the compound K-2041 as a pale yellow syrup at a yield of 31 %.

500MHz NMR 7.29-7.32(2H, m), 7.23(1H, dd, J=8.0Hz, J=8.0Hz), 6.96-6.99(2 H, m), 6.86-6.88(2H, m), 6.77-6.79(1H, m), 3.81(3H, s), 3.71(1H, q, J=7.0Hz), 2.83(2H, t, J=7.2Hz), 2.45-2.50(1H, m), 2.38-2.43(1H, m), 1.54-1.60(2H, m), 1.38-1.48(3H, m), 1.34(3H, d, J=7.0Hz), m/z=347.

Example 62: Synthesis of K-2045

[0266] 3-Bromobenzenethiol (650 mg, 3.44 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (524 mg, 3.79 mmol) and 1-bromo-2-chloroethane (0.29 ml, 3.48 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (280 mg, 2.02 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (420 mg, 2.78 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 120 hours.

[0267] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 185 : 1) to thereby give 395 mg (1.23 mmol) of the compound K-2045 as a pale yellow syrup at a yield of 44 %.

500MHz NMR 7.43(1H, s), 7.28(1H, d, J=8.0Hz), 7.22(1H, dd, J=8.0Hz, J=8.0Hz), 7.18(1H, d, J=8.0Hz), 7.19(1H, dd, J=7.5Hz, J=7.5Hz), 6.87(1H, d, J=7.5Hz), 6.86(1H, s), 6.77(1H, dd, J=7.5Hz, J=1.5Hz), 3.80(3H, s), 3.74(1H, q, J=6.5Hz), 3.02(2H, t, J=6.5Hz), 2.66-2.77(2H, m), 1.68(1H, s), 1.34(3H, d, J=6.5Hz), m/z=365, 367.

Example 63: Synthesis of K-2046

[0268] 3-Bromobenzenethiol (580 mg, 3.06 mmol) was dissolved in acetonitrile (9.0 ml) and then potassium carbonate (432 mg, 3.13 mmol) and 1,3-dibromopropane (0.31 ml, 3.05 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (280 mg, 2.02 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (230 mg, 1.52 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0269] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 213 mg (0.56 mmol) of the compound K-2046 as a pale yellow syrup at a yield of 37 %.

500MHz NMR , 7.40-7.41(1H, m), 7.18-7.28(3H, m), 7.11(1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.88(2H, m), 6.76-6.79(1H, m), 3.80(3H, s), 3.72(1H, q, J=7.0Hz), 2.88(2H, m), 2.49-2.54(1H, m), 2.41-2.46(1H, m), 1.54-1.69(2H, m), 1.34(3H, d, J=7.0Hz), m/z=379, 381.

Example 64: Synthesis of K-2047

[0270] 3-Bromobenzenethiol (470 mg, 2.49 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (347 mg, 2.51 mmol) and 1,4-dibromobutane (0.30 ml, 2.51 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (320 mg, 2.32 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (200 mg, 1.32 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0271] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 185 mg (0.47 mmol) of the compound K-2047 as a pale yellow syrup at a yield of 36 %.

500MHz NMR 7.19-7.28(3H, m), 7.02-7.13(2H, m), 6.86-6.88(2H, m), 6.76-6.79(1H, m), 3.81(3H, s), 3.77(1H, q, J=6.5Hz), 1.76-1.79(2H, m), 2.89-3.01(2H, m), 2.60-2.65(1H, m), 2.51-2.56(1H, m), 2.31-2.42(2H, m), 1.52(1H, s), 1.33(3H, d, J=6.5Hz), m/z=393, 395.

Example 65: Synthesis of K-2048

[0272] 3-Bromobenzenethiol (530 mg, 2.80 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (395 mg, 2.86 mmol) and 1,5-dibromopentane (0.38 ml, 2.78 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (213 mg, 1.54 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (200 mg, 1.32 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0273] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 226 mg (0.55 mmol) of the compound K-2048 as a pale yellow syrup at a yield of 42 %.

500MHz NMR 7.41(1H, s), 7.18-7.28(3H, m), 7.11 (1H, dd, J=7.5Hz, J=7.5Hz), 6.88(1H, d, J=7.5Hz), 6.87(1H, s), 6.78(1H, dd, J=7.5Hz, J=2.5Hz), 3.81(3H, s), 3.72(1H, q, J=6.5Hz), 2.89(2H, q, J=7.2Hz), 2.47-2.51(1H, m), 2.40-2.43(1H, m), 1.62(2H, m), 1.40-1.50(5H, m), 1.234(3H, d, J=6.5Hz).

Example 66: Synthesis of K-2049

[0274] 3-Bromobenzenethiol (600 mg, 3.17 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (500 mg, 3.62 mmol) and 1,6-dibromohexane (0.50 ml, 3.25 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (205 mg, 1.48 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.66 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0275] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 267 mg (0.63 mmol) of the compound K-2049 as a pale yellow syrup at a yield of 38 %.

500MHz NMR 7.41(1H, dd, J=1.8Hz, J=1.8Hz), 7.19-7.27(3H, m), 7.11(1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.89(2H, m), 6.77(1H, dd, J=8.0Hz, J=2.5Hz), 3.81(3H, s), 3.72(1H, t, J=6.5Hz), 2.88(2H, t, J=7.8Hz), 2.39-2.51(2H, m), 1.50-1.65(2H, m), 1.25-1.49(7H, m), 1.34(3H, d, J=6.5Hz).

Example 67: Synthesis of K-2050

[0276] 3-Bromobenzenethiol (525 mg, 2.78 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (325 mg, 2.36 mmol) and 1,7-dibromoheptane (0.47 ml, 2.75 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (182 mg, 1.32 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (210 mg, 1.39 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0277] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 260 mg (0.60 mmol) of the compound K-2050 as a pale yellow syrup at a yield of 43 %.

500MHz NMR 7.41(1H, dd, J=2.0Hz, J=2.0Hz), 7.23-7.27(2H, m), 7.18-7.21(1H, m), 7.11(1H, dd, J=8.0Hz, J=8.0Hz), 6.90-6.93(2H, m), 6.80(1H, dd, J=8.0Hz, J=2.5Hz), 3.82(3H, s), 3.77-3.80(1H, m), 2.88(2H, t, J=7.5Hz), 2.42-2.54(2H, m), 1.58-1.64(2H, m), 1.50-1.55(1H, m), 1.35-1.45(4H, m), 1.42(3H, d, J=7.5Hz), 1.21-1.29(4H, m), m/z=4.35, 437.

Example 68: Synthesis of K-2051

[0278] 3-Bromobenzenethiol (610 mg, 3.22 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (490 mg, 3.55 mmol) and 1,8-dibromooctane (0.59 ml, 3.20 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (218 mg, 1.58 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.66 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0279] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 170 mg (0.38 mmol) of the compound K-2051 as a pale yellow syrup at a yield of 24 %.

500MHz NMR 7.41-7.42(1H, m), 7.19-7.27(3H, m), 7.11(1H, dd, J=7.8Hz, J=7.8Hz), 6.90-6.92(2H, m), 6.79(1H, dd, J=7.8Hz, J=2.0Hz), 3.82(3H, s), 3.76-3.82(1H, m), 2.89(2H, t, J=7.8Hz), 2.42-2.53(2H, m), 1.59-1.65(2H, m), 1.49(1H, m), 1.41(3H, d, J=6.5Hz), 1.36-1.43(4H, m), 1.22-1.28(6H, m), m/z=449, 451.

Example 69: Synthesis of K-2052 (N-{5-[(4-fuluorophenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0280] 4-Fluorobenzenethiol (460 mg, 3.60 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (500 mg, 3.62 mmol) and 1,5-dibromopentane (0.50 ml, 3.67 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (210 mg, 1.52 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (300 mg, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0281] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 210 mg (0.57 mmol) of the compound K-2052 as a pale yellow syrup at a yield of 31 %.

500MHz NMR 8.17(1H, d, J=8.0Hz), 7.87(1H, d, J=8.5Hz), 7.74(1H, d, J=8.0Hz), 7.62(1H, d, J=8.0Hz), 7.41-7.50(5H, m), 7.29(2H, d, J=8.5Hz), 4.61(1H, q, J=6.5Hz), 2.82(2H, t, J=7.5Hz), 2.56-2.57(2H, m), 2.37-2.43(2H, m), 1.40-1.59(5H, m), 1.46(3H, d, J=6.5Hz), m/z=367.

Example 70: Synthesis of K-2055

[0282] 4-Trifluoromethylbenzenethiol (408 mg, 2.29 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (330 mg, 2.39 mmol) and 1,3-dibromopropane (0.23 ml, 2.28 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (172 mg, 1.25 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (210 mg, 1.39 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0283] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 122 mg (0.33 mmol) of the compound K-2055 as a pale yellow syrup at a yield of 24 %.

500MHz NMR 7.44-7.50(2H, m), 7.32(1H, d, J=8.5Hz), 7.23(1H, dd, J=8.5Hz, J=8.5Hz), 7.17-7.20(1H, m), 6.85-6.88(2H, m), 6.77-6.79(1H, m), 3.80(3H, s), 3.70-3.74(1H, m), 1.77-1.83(2H, m), 1.34(3H, d, J=6.5Hz), 1.25-1.26(1H, m), m/z=369.

Example 71: Synthesis of K-2056

[0284] 4-Trifluoromethylbenzenethiol (487 mg, 2.74 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (374 mg, 2.71 mmol) and 1,4-dibromobutane (0.33 ml, 2.77 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (172 mg, 1.25 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.65 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0285] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 152 mg (0.40 mmol) of the compound K-2056 as a pale yellow syrup at a yield of 24 %.

500MHz NMR 7.49(2H, d, J=8.5Hz), 7.32(2H, d, J=8.0Hz), 7.23(1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.88(2H, m), 6.76-6.79(1H, m), 3.80(1H, s), 3.71(1H, q, J=6.5Hz), 2.92-2.95(2H, t, J=7.5Hz), 1.55-1.73(4H, m), 1.47(1H, s), 1.33(3H, d, J=6.5Hz), 2.50-2.55(1H, m), 2.42-2.47(1H, m), m/z=383.

Example 72: Synthesis of K-2057

[0286] 4-Trifluoromethylbenzenethiol (560 mg, 3.15 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (440 mg, 3.19 mmol) and 1,5-dibromopentane (0.43 ml, 3.16 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (240 mg, 1.74 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (290 mg, 1.92 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0287] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 129 mg (0.32 mmol) of the compound K-2057 as a pale yellow syrup at a yield of 17 %.

500MHz NMR 7.49(2H, d, J=8.5Hz), 7.31(2H, d, J=8.0Hz), 7.23(1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.89(2H, m), 6.76-6.79(1H, m), 3.81(3H, s), 3.71(1H, q, J=6.8Hz), 2.94(2H, t, J=7.3Hz), 2.40-2.51(2H, m), 1.63-1.68(2H, m), 1.42-1.51(5H, m), 14.34(3H, d, J=6.8Hz), m/z=397.

Example 73: Synthesis of K-2058

[0288] 4-Trifluoromethylbenzenethiol (500 mg, 2.81 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (420 mg, 3.64 mmol) and 1,6-dibromohexane (0.43 ml, 2.79 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (150 mg, 1.09 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (260 mg, 1.72 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0289] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 155 mg (0.38 mmol) of the compound K-2058 as a pale yellow syrup at a yield of 22 %.

500MHz NMR 7.49(2H, d, J=8.5Hz), 7.32(2H, d, J=7.0Hz), 7.23(1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.89(2H, m), 6.76-6.79(1H, m), 3.81(3H, s), 3.72(1H, q, J=6.5Hz), 2.94(2H, t, J=7.5Hz), 2.39-2.52(2H, m), 1.63-1.69(2H, m), 1.39-1.50(5H, m), 1.29-1.34(2H, m), 1.34(3H, d, J=6.5Hz), m/z=411.

Example 74: Synthesis of K-2059

[0290] 4-Trifluoromethylbenzenethiol (500 mg, 2.81 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (420 mg, 3.64 mmol) and 1,7-dibromoheptane (0.48 ml, 2.81 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (150 mg, 1.09 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (260 mg, 1.72 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0291] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 204 mg (0.48 mmol) of the compound K-2059 as a pale yellow syrup at a yield of 28 %.

500MHz NMR 7.49(2H, d, J=8.5Hz), 7.32(2H, d, J=6.5Hz), 7.23(1H, dd, J=6.0Hz, J=6.0Hz), 6.87-6.89(2H, m), 6.76-6.79(1H, m), 3.81(3H, s), 3.73(1H, q, J=6.0Hz), 2.94(2H, t, J=6.5Hz), 2.39-2.51(2H, m), 1.62-1.68(2H, m), 1.34-1.48(9H, m), 1.35(3H, d, J=6.0Hz), m/z=425.

Example 75: Synthesis of K-2061

[0292] 3-Chlorobenzenethiol (460 mg, 3.18 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (440 mg, 3.19 mmol) and 1,3-dibromopropane (0.32 ml, 3.15 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (210 mg, 1.52 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (300 mg, 1.99 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0293] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 272 mg (0.81 mmol) of the compound K-2061 as a pale yellow syrup at a yield of 41 %.

500MHz NMR 7.11-7.27(5H, m), 6.86-6.88(2H, m), 6.77-6.79(1H, m), 3.81(3H, s), 3.70(1H, q, J=6.5Hz), 2.89-3.01(2H, m), 2.60-2.65(1H, m), 2.51-2.56(1H, m), 1.75-1.81(2H, m), 1.47(1H, s), 1.33(3H, d, J=6.5Hz), m/z=335.

Example 76: Synthesis of K-2066

[0294] 2,5-Dichlorobenzenethiol (575 mg, 3.21 mmol) was dissolved in acetonitrile (11.0 ml) and then potassium carbonate (440 mg, 3.19 mmol) and 1-bromo-2-chloroethane (0.26 ml, 3.12 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (225 mg, 1.63 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (340 mg, 2.25 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 100 hours.

[0295] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 182 mg (0.51 mmol) of the compound K-2066 as a pale yellow syrup at a yield of 23 %.

500MHz NMR 7.21-7.30(3H, m), 7.19(1H, d, J=2.5Hz), 6.88-6.89(2H, m), 6.77(1H, dd, J=8.5Hz, J=2.5Hz), 3.81(3H, s), 3.76(1H, q, J=6.5hZ), 3.04(2H, t, J=7.0Hz), 2.72-2.83(2H, m), 1.66(1H, s), 1.36(3H, d, J=6.5Hz), m/z=355, 357.

Example 77: Synthesis of K-2075

[0296] 2-Bromobenzenethiol (702 mg, 3.71 mmol) was dissolved in acetonitrile (14.0 ml) and then potassium carbonate (525 mg, 3.80 mmol) and 1,5-dibromopentane (0.50 ml, 3.67 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (247 mg, 1.79 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0297] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give 144 mg (0.34 mmol) of the compound K-2075 as a pale yellow syrup at a yield of 18%.

500MHz NMR 8.18(1H, d, J=8.5Hz), 7.87(1H, d, J=8.5Hz), 7.64(1H, d, J=8.5Hz), 7.74(1H, d, J=8.5Hz), 7.45-7.53(4H, m), 7.13-7.25(2H, m), 6.99(1H, ddd, J=1.5Hz, J=6.0Hz, J=6.0Hz), 4.62(1H, q, J=7.0Hz), 2.89(2H, t, J=7.5Hz), 2.52-2.63(2H, m), 1.66-1.71(2H, m), 1.45-1.59(5H, m), 1.49(3H, d, J=7.0Hz), m/z=427.

Example 78: Synthesis of K-2076 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-{[4-(trifluoromethyl)phenyl]thio}pentyl)amine)

[0298] 4-Trifluoromethylbenzenethiol (510 mg, 2.861 mmol) was dissolved in acetonitrile (12.0 ml) and then potassium carbonate (400 mg, 2.89 mmol) and 1,5-dibromopentane (0.39 ml, 2.86 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (200 mg, 1.45 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.28 ml, 1.73 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0299] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 180 : 1) to thereby give 53 mg (0.13 mmol) of the compound K-2076 as a pale yellow syrup at a yield of 7 %.

500MHz NMR 8.18(1H, d, J=8.5Hz), 7.87(1H, d, J=7.0Hz), 7.74(1H, d, J=6.5Hz), 7.63(1H, d, J=6.5Hz), 7.45-7.52(5H, m), 7.30(2H, d, J=8.0Hz), 4.62(1H, q, J=6.5Hz), 2.93(2H, t, J=6.5Hz), 2.93(2H, t, J=7.0Hz), 2.51-2.63(2H, m), 1.63-1.69(2H, m), 1.44-1.56(5H, m), 1.49(3H, d, J=6.5Hz), m/z=417.

Example 79: Synthesis of K-2078

[0300] 3,4-Dichlorobenzenethiol (469 mg, 2.62 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (400 mg, 2.89 mmol) and 1,3-dibromopropane (0.27 ml, 2.67 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (180 mg, 1.30 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (240 mg, 1.59 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0301] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 143 mg (0.39 mmol) of the compound K-2078 as a pale yellow syrup at a yield of 25 %.

500MHz NMR 7.36(1H, d, J=1.5Hz), 7.31(1H, d, J=8.5Hz), 7.24(1H, dd, J=6.5Hz, J=6.5Hz), 7.10(1H, dd, J=8.5Hz, J=1.5Hz), 6.85-6.88(2H, m), 6.77-6.79(1H, , m), 3.81(3H, s), 3.71(1H, q, J=6.5Hz), 2.88-3.00(2H, m), 2.50-2.64(2H, m), 1.71-1.81(2H, m), 1.52(1H, s), 1.33(3H, d, J=6.5Hz), m/z=369, 371.

Example 80: Synthesis of K-2079

[0302] 3,4-Dichorobenzenethiol (556 mg, 3.11 mmol) was dissolved in acetonitrile (12.0 ml) and then potassium carbonate (412 mg, 2.99 mmol) and 1,4-dibromobutane (0.37 ml, 3.10 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (242 mg, 1.75 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (280 mg, 1.85 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0303] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 156 mg (0.41 mmol) of the compound K-2079 as a pale yellow syrup at a yield of 22 %.

500MHz NMR 7.34(1H, d, J=2.5Hz), 7.31(1H, d, J=8.5Hz), 7.23(1H, dd, J=7.5Hz, J=7.5Hz), 7.10(1H, dd, J=8.5Hz, J=2.5Hz), 6.87(1H, d, J=7.5Hz), 6.86(1H, s), 6.76-6.79(1H, m), 3.80(3H, s), 3.71(1H, q, J=7.0Hz), 2.87(2H, t, J=7.0Hz), 2.41-2.54(2H, m), 1.53-1.68(4H, m), 1.46(1H, s), 1.33(3H, d, J=7.0Hz), m/z=383, 385.

Example 81: Synthesis of K-2080

[0304] 3,4-Dichlorobenzenethiol (515 mg, 2.88 mmol) was dissolved in acetonitrile (11.0 ml) and then potassium carbonate (410 mg, 2.97 mmol) and 1,5-dibromopentane (0.39 ml, 2.86 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (230 mg, 1.66 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (260 mg, 1.72 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0305] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 250 mg (0.63 mmol) of the compound K-2080 as a pale yellow syrup at a yield of 37 %.

500MHz NMR 7.34(1H, d, J=2.5Hz), 7.31(1H, d, J=8.5Hz), 7.22-7.25(1H, m), 7.09(1H, dd, J=2.5Hz, J=8.5Hz), 6.88(1H, d, J=8.5Hz), 6.87(1H, s), 6.78(1H, dd, J=8.5Hz, J=2.5Hz), 3.81(3H, s), 3.72(1H, q, J=6.5Hz), 2.87(2H, t, J=8.0Hz), 2.39-2.52(2H, m), 1.59-1.64(2H, m), 1.38-1.51(5H, m), 1.34(3H, d, J=6.5Hz), m/z=395, 397.

Example 82: Synthesis of K-2082

[0306] 3,4-Dichlorobenzenethiol (720 mg, 4.02 mmol) was dissolved in acetonitrile (15.0 ml) and then potassium carbonate (550 mg, 3.98 mmol) and 1,7-dibromoheptane (0.64 ml, 3.75 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (230 mg, 1.66 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (360 mg, 2.38 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0307] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 253 mg (0.59 mmol) of the compound K-2082 as a pale yellow syrup at a yield of 25 %.

500MHz NMR 7.35(1H, d, J=2.5Hz), 7.31(1H, d, J=8.0Hz), 7.22-7.25(1H, m), 7.10(1H, dd, J=8.5Hz, J=2.5Hz), 6.88-6.90(1H, m), 6.90(1H, s), 6.78(1H, dd, J=2.5Hz, J=8.5Hz), 3.81(3H, s), 3.75(1H, q, J=6.5Hz), 2.87(2H, t, J=7.3Hz), 2.40-2.52(2H, m), 1.58-1.64(2H, m), 1.48(1H, s), 1.34-1.64(2H, m), 1.37(3H, d, J=6.5Hz), 1.24-1.33(4H, m), m/z=425, 427.

Example 83: Synthesis of K-2084

[0308] 2,6-Dichlorobenzenethiol (540 mg, 3.02 mmol) was dissolved in acetonitrile (11.0 ml) and then potassium carbonate (420 mg, 3.04 mmol) and 1,3-dibromopropane (0.31 ml, 3.05 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (234 mg, 1.69 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (230 mg, 1.52 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0309] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 182 mg (0.49 mmol) of the compound K-2084 as a pale yellow syrup at a yield of 32 %.

500MHz NMR 7.6(2H, d, J=8.0Hz), 7.22(1H, dd, J=8.0Hz, J=8.0Hz), 7.16(1H, dd, J=8.0Hz, J=8.0Hz), 6.86(1H, d, J=8.0Hz), 6.85(1H, s), 6.76-6.78(1H, m), 3.81(3H, s), 3.70(1H, q, J=6.0Hz), 2.89-2.98(2H, m), 2.52-2.64(2H, m), 1.65-1.71(2H, , m), 1.46(1H, s), 1.32(3H, d, J=6.0Hz), m/z=369, 371.

Example 84: Synthesis of K-2085

[0310] 2,6-Dichlorobenzenethiol (500 mg, 2.79 mmol) was dissolved in acetonitrile (10.0 ml) and then potassium carbonate (400 mg, 2.90 mmol) and 1,4-dibromobutane (0.33 ml, 2.76 mmol) were successively added thereto at room temperature. The resulting mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (230 mg, 1.65 mmol) and (R)-(+)-3-methoxy-α-methylbenzylamine (250 mg, 1.65 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 24 hours.

[0311] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 293 mg (0.76 mmol) of the compound K-2085 as a pale yellow syrup at a yield of 46%.

500MHz NMR 7.36(2H, d, J=7.5Hz), 7.23(1H, dd, J=7.5Hz, J=7.5Hz), 7.16(1H, dd, J=8.0Hz, J=8.0Hz), 6.85-6.87(1H, m), 6.86(1H, s), 6.76-6.78(1H, m), 3.81(3H, s), 3.70(1H, q, J=6.5Hz), 2.89(2H, t, J=7.0Hz), 2.38-2.51(2H, m), 1.51-1.63(4H, m), 1.49(1H, s), 1.32(3H, d, J=6.5Hz).

Example 85: Synthesis of K-2087 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-{[3-(trifluoromethyl)phenyl]thio}butyl)amine)

[0312] 3-Trifluoromethylbenzenethiol (670 mg, 3.76 mmol) was dissolved in acetonitrile (14.0 ml) and then potassium carbonate (516 mg, 3.73 mmol) and 1,4-dibromobutane (0.45 ml, 3.77 mmol) were successively added thereto at room temperature. The resulting mixture was stirred under ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (300 mg, 2.17 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 12 hours.

[0313] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 150 : 1) to thereby give 298 mg (0.74 mmol) of the compound K-2087 as a pale yellow syrup at a yield of 40 %.

500MHz NMR 8.18(1H, d, J=8.0Hz), 7.86-7.88(1H, m), 7.74(1H, d, J=8.0Hz), 7.63(1H, d, J=7.5Hz), 7.45-7.52(4H, m), 7.41-7.43(1H, m), 7.33-7.39(2H, m), 4.62(1H, q, J=6.5Hz), 2.92(2H, d, J=7.0Hz), 2.60-2.65(1H, m), 2.52-2.57(1H, m), 1.63-1.72(4H, m), 4.54(1H, s), 1.48(3H, d, J=6.5Hz), m/z=403.

Example 86: Synthesis of K-2117 ((R)-N-[1-(1'-naphthyl)ethyl]-2-(2',5'-dichlorophenylthio)ethylamine)

[0314] 2,5-Dichlorobenzenethiol (5.10 g, 28.5 mmol) was dissolved in acetonitrile (30 ml) and then potassium carbonate (4.20 g, 30.4 mmol) and 1-bromo-2-chloroethane (2.45 ml, 29.4 mmol) were successively added thereto at room temperature. The resulting mixture was stirred under ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (4.0 g, 28.9 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (3.70 ml, 22.9 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at 100 °C for additional 120 hours.

[0315] After the completion of the reaction, the reaction mixture was cooled by allowing to stand at room temperature. After pouring water thereinto, the mixture was subjected to separatory extraction with chloroform and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give 5.70 g (15.2 mmol) of the compound K-2117 as a pale yellow syrup at a yield of 66 %.

500MHz NMR 8.17(1H, d, J=8.5Hz), 7.85-7.87(1H, m), 7.73(1H, d, J=8.0Hz), 7.65(1H, d, J=7.5Hz), 7.44-7.52(4H, m), 7.26(1H, d, J=8.5Hz), 7.20(1H, d, J=2.5Hz), 7.05(1H, dd, J=2.5Hz, J=8.5Hz), 4.65(1H, q, J=6.5Hz), 3.09(2H, m), 2.82-2.91(2H, m), 1.68(1H, s), 1.51(3H, d, J=6.5Hz), m/z=375, 377.

Example 87: Synthesis of K-2117 hydrochloride

[0316] The compound K-2117 (7.01 g, 18.6 mmol) was dissolved in a 30 % hydrochloric acid-methanol solution (HCl-MeOH) (40 ml) and stirred at room temperature for 5 minutes.

[0317] After the completion of the reaction, the reaction system was concentrated in situ under reduced pressure to thereby completely remove the hydrochloric acid-methanol solution. The residue was filtered through a Kiriyama funnel and the resulting crystals were washed with hexane. Thus 5.87 g (14.2 mmol) of K-2117 hydrochloride was obtained in the form of white crystals at a yield of 76 %.

m/z=375, 377. ^{1}H-NMR (400MHz) 10.97 (1H, bs), 10.30 (1H, bs), 8.18 (1H, d, J=7.32Hz), 7.88-7.97 (3H, m), 7.53-7.66 (3H, m), 7.31 (1H, d, J=2.4Hz), 7.14 (1H, d, J=8.56Hz), 7.01 (1H, dd, J=1.36Hz, J=8.56Hz), 5.23-5.27 (1H, m), 3.55-3.61 (2H, m), 2.95-3.10 (2H, m), 2.04 (3H, d, J=6.60Hz).

Example 88: Synthesis of K-2177

[0318] Dibenzylamine (1.0 g, 0.51 mmol) and triethylamine (0.85 ml, 0.61 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (0.505 g, 0.56 mmol, 1.1 mol eq.) was added under-ice cooling thereto. The resulting mixture was stirred at room temperature for 30 minutes.

[0319] After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography (silica gel, chloroform-methanol) to thereby give colorless prisms (1.085 g, 85.0 %).

[0320] The compound thus obtained (50 mg, 0.20 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (41.0 mg, 0.24 mmol, 1.2 mol eq.) were dissolved in chloroform-methanol (2 ml) and allowed to stand at room temperature for 1 week.

[0321] After the completion of the reaction, the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography (silica gel, chloroform-methanol) to thereby give 50.9 mg of K-2177 as a colorless oil at a yield of 60.5 %.

MS m/z: 422(M^+). ^{1}H-NMR δ: 1.53(3H, d, J=6.7Hz, C$\underline{H}_3$), 2.60-2.70(2H, m, C$\underline{H}_2$), 2.86-2.96(2H, m, C$\underline{H}_2$), 4.42(2H, s, C$\underline{H}_2$), 4.62(2H, s, C$\underline{H}_2$), 4.69(1H, q, J=6.7Hz, C$\underline{H}$), 7.13(2H, d, J=7.3Hz, Ar-$\underline{H}$), 7.21(2H, d, J=6.7Hz, Ar-$\underline{H}$), 7.27-7.36(6H, m, Ar-$\underline{H}$), 7.45-7.50(3H, m, Ar-$\underline{H}$), 7.70(1H, d, J=6.7Hz, Ar-$\underline{H}$), 7.74(1H, d, J=7.9Hz, Ar-$\underline{H}$), 7.86(1H, dd, J=1.8, 6.7Hz, Ar-$\underline{H}$), 8.16(1H, d, J=7.9Hz, Ar-$\underline{H}$).

Example 89: Synthesis of K-2246 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-{[4-(trifluoromethyl)phenyl]thio}butyl)amine)

[0322] 960 mg (5.39 mmol) of 4-trifluoromethylthiophenol was dissolved in 8 ml of acetonitrile. Subsequently, 802 mg (5.80 mmol) of potassium carbonate and 0.65 ml (5.44 mmol) of 1,4-dibromobutane were added thereto at room temperature and the obtained mixture was stirred at the same temperature for 30 minutes. After confirming the completion of the reaction by TLC, 5 ml of acetonitrile, 693 mg (5.01 mmol) of potassium carbonate and 0.49 ml (2.96 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85 °C for 12 hours.

[0323] After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was poured thereinto. Next, it was subjected to separating extraction with chloroform and a saturated aqueous solution of sodium chloride and the organic layer thus obtained was dried over sodium sulfate. Further, the organic layer was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (80 g, chloroform/methanol = 200/1) to thereby give 210 mg (0.52 mmol, 17.6 %) of K-2246 as a pale yellow transparent syrup.

[0324] Subsequently, the K-2246 thus obtained was dissolved in a 10 % solution of hydrochloric acid in methanol, stirred for 5 minutes and then concentrated as such under reduced pressure. The crystals thus formed were washed with diethyl ether to thereby give 104 mg (0.24 mmol, 8.1 %) of K-2246 hydrochloride as white crystals.

^{1}H-NMR (400MHz) 10.6 (1H, bs), 10.1 (1H, bs), 8.24 (1H, d, J=7.08Hz), 7.99 (1H, d, J=8.52Hz), 7.90-7.96 (2H, m), 7.55-7.67 (3H, m), 7.39-7.41 (2H, m), 7.17-7.19 (2H, m), 5.17-5.24 (1H, m), 2.73-2.84 (4H, m), 2.11-2.18 (2H, m), 2.06 (3H, d, J=6.60Hz), 1.57-1.62 (4H, m), m/z=403.

Example 90: Synthesis of K-2076:

[0325] 1.040 g (5.83 mmol) of 4-trifluoromethylthiophenol was dissolved in 10 ml of acetonitrile. Subsequently, 1.024

g (7.40 mmol) of potassium carbonate and 0.80 ml (5.87 mmol) of 1,5-dibromopentane were added thereto at room temperature and the obtained mixture was stirred at the same temperature for 1 hour. After confirming the completion of the reaction by TLC, 8 ml of acetonitrile, 853 mg (6.17 mmol) of potassium carbonate and 0.60 ml (3.63 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85 °C for 12 hours.

[0326] After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was poured thereinto. Next, it was subjected to separating extraction with chloroform and a saturated aqueous solution of sodium chloride and the organic layer thus obtained was dried over sodium sulfate. Further, the organic layer was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (100 g, chloroform/methanol = 200/1) to thereby give 240 mg (0.57 mmol, 17.7 %) of K-2076 as a pale yellow transparent syrup.

[0327] Subsequently, the K-2076 thus obtained was dissolved in a 10 % solution of hydrochloric acid in methanol, stirred for 5 minutes and then concentrated as such under reduced pressure. The crystals thus formed were washed with diethyl ether to thereby give 115 mg (0.25 mmol, 6.9 %) of K-2076 hydrochloride as white crystals.

^{1}H-NMR (400MHz) 10.55 (1H, bs), 10.01 (1H, bs), 8.24 (1H, d, J=7.08Hz), 7.89-7.99 (3H, m), 7.52-7.66 (3H, m), 7.44 (2H, d, J=8.32Hz), 7.23 (2H, d, J=8.32Hz), 5.19 (1H, bs), 2.82 (2H, t, J=7.08Hz), 2.74 (2H, bs), 2.04 (3H, d, J=6.36Hz), 1.96-2.04 (2H, m), 1.50-1.57 (2H, m), 1.30-1.38 (2H, m), m/z=417.

Example 91: Synthesis of K-2243 (N1,N1-di(4-chlorobenzyl)-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0328] To 500 mg (3.56 mmol) of p-chlorobenzaldehyde and 503.6 mg (3.56 mmol, 1.0 mol eq.) of p-chlorobenzylamine was added 1.26 ml (4.27 mmol, 1.2 mol eq.) of titanium tetraisopropoxide and the obtained mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in methanol and 538.7 mg (14.24 mmol, 4.0 mol eq.) of sodium boron hydride was added thereto. The obtained mixture was stirred at room temperature for 12 hours.

[0329] After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue, and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained oil was purified by column chromatography (silica gel, chloroform) to thereby give 819 mg (86.6 %) of the compound 124 as a colorless oil.

MS m/z:266. ^{1}H-NMR δ:3.74 (4H, d, J=2.7, $C\underline{H}_2$x2), 7.24-7.30 (8H, m, Ar-H).

[0330] 500 mg (1.88 mmol) of the above-mentioned compound 124 and 0.31 ml (2.26 mmol, 1.2 mol eq.) of triethylamine were dissolved in chloroform and 187.1 mg (2.07 mmol, 1.1 mol eq.) of acryloyl chloride was added thereto under ice-cooling. The obtained mixture was then stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained oil was purified by column chromatography (silica gel, chloroform) to thereby give 570.3 mg (94.4 %) of the compound 125 as a colorless oil.

MS m/z:320. ^{1}H-NMR δ:4.47 (2H, s, $C\underline{H}_2$), 4.59 (2H, s, $C\underline{H}_2$), 5.77 (1H, dd, J=2.7, 9.8Hz, CH=C$\underline{H}_2$), 6.52(1H, d, J=2.7Hz, C$\underline{H}$=CH_2), 6.54 (1H, d, J=9.8Hz, CH=C$\underline{H}_2$), 7.08 (2H, d, J=8.1Hz, Ar-H), 7.18 (2H, d, J=8.1Hz, Ar-H), 7.29 (2H, d, J=8.1Hz, Ar-H), 7.33 (2H, d, J=8.1Hz, Ar-H).

[0331] 100 mg (0.31 mmol) of the above-mentioned compound 125 and 64.2 mg (0.38 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography (silica gel, chloroform) to thereby give 106.6 mg (69.5 %) of K-2243 as a colorless oil.

MS m/z:491. ^{1}H-NMR δ:1.51 (3H, d, J=6.6Hz, $C\underline{H}_3$), 2.60 (2H, t, J=6.1Hz, $C\underline{H}_2$), 2.84-2.96 (2H, m, $C\underline{H}_2$), 4.35 (2H, s, $C\underline{H}_2$), 4.53 (2H, s, $C\underline{H}_2$), 4.66 (1H, q, J=6.6Hz, C$\underline{H}$), 7.03 (2H, d, J=8.3Hz, Ar-H), 7.12 (2H, d, J=8.3Hz, Ar-H), 7.27 (2H, d, J=8.3Hz, Ar-H), 7.30 (2H, d, J=8.3Hz, Ar-H), 7.47 (1H, t, J=5.1Hz, Ar-H), 7.48 (1H, t, J=5.1Hz, Ar-H), 7.49 (1H, t, J=5.1Hz, Ar-H), 7.67 (1H, d, J=5.1Hz, Ar-H), 7.74 (1H d, J=5.1Hz, Ar-H), 7.87 (1H, d, J=7.5Hz, Ar-H), 7.16 (1H, d, J=7.5Hz, Ar-H).

Example 92: Synthesis of K-2257 (N1,N1-di[4-(trifluoromethoxy)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0332] To 500 mg (2.62 mmol) of p-(trifluoromethoxy)benzylamine and 497.3 mg (2.62 mmol, 1.0 mol eq.) of p-(trifluoromethoxy)-benzaldehyde was added 0.926 ml (3.14 mmol, 1.2 mol eq.) of titanium tetraisopropoxide and the obtained mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in methanol and 396.5 mg (10.48 mmol, 4.0 mol eq.) of sodium boron hydride was added thereto. The obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained oil was purified by column chromatography (silica gel, chloroform) to thereby give 835.2 mg (87.5 %) of the compound 126 as a colorless oil.

MS m/z:365. ^{1}H-NMR δ:3.80 (4H, s, $\underline{CH_2}$x2), 7.17 (4H, d, J=8.1Hz, Ar-H), 7.36 (4H, d, J=8.1Hz, Ar-H).

[0333] 500 mg (1.37 mmol) of the above-mentioned compound 126 and 0.23 ml (1.64 mmol, 1.2 mol eq.) of triethylamine were dissolved in chloroform and 136.3 mg (1.51 mmol, 1.1 mol eq.) of acryloyl chloride was added thereto under ice-cooling. The obtained mixture was then stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained oil was purified by column chromatography (silica gel, chloroform) to thereby give 519.3 mg (90.5 %) of the compound 127 as a colorless oil.

MS m/z:419. ^{1}H-NMR δ:4.53 (2H, s, $C\underline{H_2}$), 4.64 (2H, s, $C\underline{H_2}$), 5.79 (1H, dd, J=2.7, 9.5Hz, CH=C$\underline{H_2}$), 6.53 (1H, d, J=2.7Hz, C$\underline{H}$=CH_2), 6.56 (1H, d, J=9.5Hz, CH=C$\underline{H_2}$), 7.15-7.31 (8H, m, Ar-H).

[0334] 450 mg (1.07 mmol) of the above-mentioned compound 127 and 220.7 mg (1.29 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography (silica gel, chloroform) to thereby give 363 mg (57.3 %) of K-2257 as a colorless oil.

MS m/z:590. ^{1}H-NMR δ:1.50 (3H, d, J=6.6Hz, $C\underline{H_3}$), 2.60 (2H, t, J=5.9Hz, $C\underline{H_2}$), 2.84-2.97 (2H, m, $C\underline{H_2}$), 4.41 (2H, s, $C\underline{H_2}$), 4.57 (2H, s, $C\underline{H_2}$), 6.65 (1H, q, J=6.6Hz, C$\underline{H}$), 7.12-7.29 (8H, m, Ar-H), 7.44-7.51 (3H, m, Ar-H), 7.66 (1H, d, J=6.8Hz, Ar-H), 7.73 (1H, d, J=8.3Hz, Ar-H), 7.86 (1H, dd, J=2.4, 7.1Hz, Ar-H), 8.17 (1H, d, J=7.1Hz, Ar-H).

Example 93: Synthesis of K-2259 (N1,N1-di[4-(trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0335] To 500 mg (2.85 mmol) of p-(trifluoromethyl)benzylamine and 497.1 mg (2.85 mmol, 1.0 mol eq.) of p-(trifluoromethyl)- benzaldehyde was added 1.01 ml (3.43 mmol, 1.2 mol eq.) of titanium tetraisopropoxide and the obtained mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in methanol and 431.3 mg (11.4 mmol, 4.0 mol eq.) of sodium boron hydride was added thereto. The obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained oil was purified by column chromatography (silica gel, chloroform) to thereby give 458.7 mg (48.3 %) of the compound 128 as a colorless oil.

MS m/z:333. ^{1}H-NMR δ:3.86 (4H, s, $\underline{CH_2}$x2), 7.47 (4H, d, J=8.1Hz, Ar-H), 7.59 (4H, d, J=8.1Hz, Ar-H).

[0336] 450 mg (1.35 mmol) of the above-mentioned compound 128 and 0.23 ml (1.62 mmol, 1.2 mol eq.) of triethylamine were dissolved in chloroform and 134.4 mg (1.48 mmol, 1.1 mol eq.) of acryloyl chloride was added thereto under ice-cooling. The obtained mixture was then stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling

off the solvent under reduced pressure, the obtained oil was purified by column chromatography (silica gel, chloroform) to thereby give 519.3 mg (99.3 %) of the compound 129 as a colorless oil.

MS m/z:387. ^{1}H-NMR δ:4.59 (2H, s, C$\underline{H}_2$), 4.70 (2H, s, C$\underline{H}_2$), 5.80 (1H, dd, J=3.7, 8.8Hz, CH=C$\underline{H}_2$), 6.54 (1H, d, J=3.7Hz, C$\underline{H}$=CH$_2$), 6.56 (1H, d, J=8.8Hz, CH=C$\underline{H}_2$), 7.23-7.64 (8H, m, Ar-H).

[0337] 800 mg (2.06 mmol) of the above-mentioned compound 129 and 424.0 mg (2.48 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography (silica gel, chloroform) to thereby give 580.7 mg (50.3 %) of K-2259 as a colorless oil.

MS m/z:558. ^{1}H-NMR δ:1.51 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.60 (2H, t, J=6.1Hz, C$\underline{H}_2$), 2.85-2.98 (2H, m, CH$_2$), 4.47 (2H, s, C$\underline{H}_2$), 4.64 (2H, s, C$\underline{H}_2$), 4.65 (1H, q, J=6.6Hz, C$\underline{H}$), 7.23 (2H, d, J=8.3Hz, Ar-H), 7.31 (2H, d, J=8.3Hz, Ar-H), 7.44-7.51 (3H, m, Ar-H), 7.55 (2H, d, J=8.3Hz, Ar-H), 7.59 (2H, d, J=8.3Hz, Ar-H), 7.66 (1H, d, J=8.1Hz, Ar-H), 7.74 (1H, d, J=8.1Hz, Ar-H), 7.87 (1H, dd, J=2.4, 8.1Hz, Ar-H), 8.18 (1H, dd, J=2.4, 8.1Hz, Ar-H).

Example 94: Synthesis of K-2247 (N1-benzyl-N1-(4-chlorobenzyl)-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0338] To 4-chlorobenzaldehyde (500 mg, 3.56 mmol) and benzylamine (381.2 mg, 3.56 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.26 ml, 4.27 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (538.7 mg, 14.24 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 201 (572.6 mg, 69.5 %). MS m/z:231.

[0339] The dibenzylamine compound 201 (300 mg, 1.29 mmol) and triethylamine (0.22 ml, 1.55 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (128.9 mg, 1.42 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 202 (372.1 mg, 100.0%). MS m/z: 285.

[0340] The conjugated ketone compound 202 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2247 (64.5 mg, 40.2 %).

MS m/z: 456, ^{1}H-NMR δ: 1.53 (3H, d, J=6.7Hz, C$\underline{H}_3$), 2.60-2.67 (2H, m, C$\underline{H}_2$), 2.86-2.95 (2H, m, C$\underline{H}_2$), 4.39 (2H, d, J=18.3Hz, C$\underline{H}_2$), 4.58 (2H, d, J=13.4Hz, C$\underline{H}_2$), 4.69 (1H, q, J=6.7Hz, C$\underline{H}$), 7.04 (1H, d, J=8.5Hz, Ar-H), 7.12 (1H, d, J=6.7Hz, Ar-H), 7.15 (1H, d, J=8.5Hz, Ar-H), 7.20 (1H, d, J=6.7Hz, Ar-H), 7.28-7.36 (5H, m, Ar-H), 7.46-7.51 (3H, m, Ar-H), 7.69 (1H, d, J=7.3Hz, Ar-H), 7.75 (1H, d, J=7.9Hz, Ar-H), 7.87 (1H, dd, J=1.8, 7.9Hz, Ar-H), 8.17 (1H, d, J=7.9Hz, Ar-H).

Example 95: Synthesis of K-2248

[0341] To 2-naphthaldehyde (500 mg, 3.20 mmol) and benzylamine (343.1 mg, 3.20 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.13 ml, 3.84 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (484.2 mg, 12.8 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the sol-

vent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 203 (769.1 mg, 97.1 %). MS m/z: 247.

[0342] The dibenzylamine compound 203 (500 mg, 2.02 mmol) and triethylamine (0.34 ml, 2.43 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (201.3 mg, 2.22 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 204 (579.7 mg, 95.0%). MS m/z: 301.

[0343] The conjugated ketone compound 204 (105.8 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2248 (69.8 mg, 42.0 %).

MS m/z: 472, ^{1}H-NMR δ: 1.52 (3H, dd, J=6.7, 8.5Hz, C<u>H</u>$_3$), 2.66-2.69 (2H, m, C<u>H</u>$_2$), 2.89-3.00 (2H, m, C<u>H</u>$_2$), 4.51 (2H, d, J=65.3Hz, C<u>H</u>$_2$), 4.67 (1H, q, J=36.7Hz, C<u>H</u>), 4.75 (2H, d, J=48.2Hz, C<u>H</u>$_2$), 7.16 (1H, d, J=7.3Hz, Ar-H), 7.22-7.39 (5H, m, Ar-H), 7.43-7.52 (5H, m, Ar-H), 7.58 (1H, d, J=25.6Hz, Ar-H), 7.68-7.88 (6H, m, Ar-H), 8.17 (1H, dd, J=7.9, 21 .4Hz, Ar-H).

Example 96: Synthesis of K-2249

[0344] To 2-chlorobenzaldehyde (500 mg, 3.56 mmol) and benzylamine (381.2 mg, 3.56 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.26 ml, 4.17 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (538.7 mg, 14.24 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 205 (427.7 mg, 51.9 %). MS m/z: 231.

[0345] The dibenzylamine compound 205 (300 mg, 1.29 mmol) and triethylamine (0.22 ml, 1.55 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (128.9 mg, 1.42 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 206 (358.8 mg, 96.8 %). MS m/z: 285.

[0346] The conjugated ketone compound 206 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2249 (67.8 mg., 50.8 %).

MS m/z: 456, ^{1}H-NMR δ: 1.53 (3H, dd, J=6.7, 4.3Hz, C<u>H</u>$_3$), 2.51-2.74 (2H, m, C<u>H</u>$_2$), 2.85-2.98 (2H, m, C<u>H</u>$_2$), 4.50 (2H, d, J=9.8Hz, C<u>H</u>$_2$), 4.64 (1H, s, C<u>H</u>$_2$), 4.66-4.70 (1H, m, C<u>H</u>), 4.78 (1H, s, C<u>H</u>$_2$), 7.15 (1H, d, J=7.9Hz, Ar-H), 7.19-7.39 (8H, m, Ar-H), 7.45-7.51 (3H, m, Ar-H), 7.70 (1H, t, J=7.9Hz, Ar-H), 7.74 (1H, dd, J=3.7, 7.9Hz, Ar-H), 7.87 (1H, d, J=7.3Hz, Ar-H), 8.17 (1H, t, J=7.3Hz, Ar-H).

Example 97: Synthesis of K-2250 (N1-benzyl-N1-(3,4-dichlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0347] To benzaldehyde (300 mg, 2.83 mmol) and 3,4-dichlorobenzylamine (497.7 mg, 2.83 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.00 ml, 3.39 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (428.2 mg, 11.32 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained res-

idue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 207 (568 mg, 75.5 %). MS m/z: 266.

[0348] The dibenzylamine compound 207 (300 mg, 1.13 mmol) and triethylamine (0.189 ml, 1.35 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (112.3 mg, 1.24 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 208 (358.3 mg, 99.3 %). MS m/z: 320.

[0349] The conjugated ketone compound 208 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2250 (96.5 mg, 62.9 %).

MS m/z: 491, ^{1}H-NMR δ: 1.51 (3H, d, J=6.6Hz, C<u>H</u>$_3$), 2.49-2.68 (2H, m, C<u>H</u>$_2$), 2.82-2.96 (2H, m, C<u>H</u>$_2$), 4.38 (2H, d, J=32.4Hz, C<u>H</u>$_2$), 4.54 (1H, s, C<u>H</u>$_2$), 4.67 (1H, d, J=42.5Hz, C<u>H</u>$_2$), 4.66 (1H, q, J=6.6Hz, C<u>H</u>), 7.11 (1H, d, J=6.6Hz, Ar-H), 7.19 (1H, d, J=6.8Hz, Ar-H), 7.21-7.41 (6H, m, Ar-H), 7.43-7.51 (3H, m, Ar-H), 7.67 (1H, dd, J=2.0, 7.1Hz, Ar-H), 7.74 (1H, d, J=8.3Hz, Ar-H), 7.86 (1H, dd, J=2.2, 8.1Hz, Ar-H), 8.16 (1H, d, J=7.3Hz, Ar-H).

Example 98: Synthesis of K-2251

[0350] To benzaldehyde (300 mg, 2.83 mmol) and 2,4-dichlorobenzylamine (497.7 mg, 2.83 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.00 ml, 3.39 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (428.2 mg, 11.32 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 209 (469 mg, 62.4 %). MS m/z: 266.

[0351] The dibenzylamine compound 209 (300 mg, 1.13 mmol) and triethylamine (0.189 ml, 1.35 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (112.3 mg, 1.24 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 210 (311.6 mg, 86.3%). MS m/z: 320.

[0352] The conjugated ketone compound 210 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2251 (126.7 mg, 82.6 %).

MS m/z: 491, ^{1}H-NMR δ: 1.51 (3H, dd, J=2.5, 6.6Hz C<u>H</u>$_3$), 2.51-2.53 (1H, m, C<u>H</u>$_2$), 2.64-2.68 (1H, m, C<u>H</u>$_2$), 2.84-2.96 (2H, m, C<u>H</u>$_2$), 4.46 (2H, d, J=13.4Hz, C<u>H</u>$_2$), 4.60 (1H, s, C<u>H</u>$_2$), 4.65-4.68 (1H, m, C<u>H</u>), 4.69 (1H, s, C<u>H</u>$_2$), 7.13 (1H, d, J=7.3Hz, Ar-H), 7.17-7.39 (7H, m, Ar-H), 7.44-7.50 (3H, m, Ar-H), 7.67 (1H, t, J=7.3Hz, Ar-H), 7.73 (1H, dd, J=3.7, 7.9Hz, Ar-H), 7.86 (1H, d, J=7.3Hz, Ar-H), 8.16 (1H, d, J=7.9Hz, Ar-H).

Example 99: Synthesis of K-2252

[0353] To benzaldehyde (500 mg, 4.71 mmol) and 3-chlorobenzylamine (667.2 mg, 4.71 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.67 ml, 5.65 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (712.7 mg, 18.84 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for

12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 211 (930.5 mg, 85.2 %). MS m/z: 231.

[0354] The dibenzylamine compound 211 (500 mg, 2.16 mmol) and triethylamine (0.36 ml, 2.59 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (214.8 mg, 2.37 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 212 (308.5 mg, 50.0 %). MS m/z: 285.

[0355] The conjugated ketone compound 212 (100 mg, 0.35 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (71.8 mg, 0.42 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2252 (85.0 mg, 53.2 %).

MS m/z: 456, ^{1}H-NMR δ: 1.50 (3H, d, J=6.6Hz, C<u>H</u>$_3$), 2.61 (2H, dt, J=6.1, 21.0Hz, C<u>H</u>$_2$), 2.82-2.96 (2H, m, C<u>H</u>$_2$), 4.40 (2H, d, J=19.3Hz, C<u>H</u>$_2$), 4.60 (2H, d, J=13.7Hz, C<u>H</u>$_2$), 4.66 (1H, q, J=6.6Hz, C<u>H</u>), 7.13 (2H, d, J=7.1Hz, Ar-H), 7.20-7.37 (7H, m, Ar-H), 7.43-7.51 (3H, m, Ar-H), 7.68 (1H, d, J=8.1Hz, Ar-H), 7.73 (1H, d, J=8.1Hz, Ar-H), 7.86 (1H, dd, J=2.2, 7.3Hz, Ar-H), 8.17 (1H, d, J=7.6Hz, Ar-H).

Example 100: Synthesis of K-2253

[0356] To 3-chlorobenzaldehyde (500 mg, 3.56 mmol) and 3-chlorobenzylamine (503.7 mg, 3.56 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.26 ml, 4.27 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (538.7 mg, 14.24 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 213 (756.5 mg, 80.3 %). MS m/z: 266.

[0357] The dibenzylamine compound 213 (500 mg, 1.88 mmol) and triethylamine (0.31 ml, 2.26 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (187.1 g, 2.07 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 214 (595.3 mg, 98.8%). MS m/z: 320.

[0358] The conjugated ketone compound 214 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2253 (96.5 mg, 62.9 %).

MS m/z: 491, ^{1}H-NMR δ: 1.51 (3H, d, J=6.1Hz, C<u>H</u>$_3$), 2.58 (2H, t, J=6.1Hz, C<u>H</u>$_2$), 2.85-2.97 (2H, m, C<u>H</u>$_2$), 4.38 (2H, s, C<u>H</u>$_2$), 4.57 (2H, d, J=3.1Hz, C<u>H</u>$_2$), 4.65 (1H, q, J=6.1Hz, C<u>H</u>), 6.99 (1H, d, J=5.5Hz, Ar-H), 7.08 (1H, d, J=6.1Hz, Ar-H), 7.11 (1H, s, Ar-H), 7.20 (1H, s, Ar-H), 7.23-7.27 (4H, m, Ar-H), 7.44-7.49 (3H, m, Ar-H), 7.67 (1H, d, J=7.3Hz, Ar-H), 7.72 (1H, d, J=7.9Hz, Ar-H), 7.85 (1H, d, J=7.9Hz, Ar-H), 8.18 (1H, d, J=7.9Hz, Ar-H).

Example 101: Synthesis of K-2254

[0359] To 2-chlorobenzaldehyde (500 mg, 3.56 mmol) and 2-chlorobenzylamine (503.6 mg, 3.56 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.25 ml, 4.27 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (538.7 mg, 14.2 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temper-

ature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 215 (632.6 mg, 66.9 %). MS m/z: 266.

[0360] The dibenzylamine compound 215 (400 mg, 1.50 mmol) and triethylamine (0.25 ml, 1.80 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (149.7 g, 1.65 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 216 (391.7 mg, 81.2 %). MS m/z: 320.

[0361] The conjugated ketone compound 216 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2254 (72.7 mg, 47.4 %).

MS m/z: 491, ^{1}H-NMR δ: 1.49 (3H, d, J=6.6Hz, C<u>H</u>$_3$), 2.53-2.60 (2H, m, C<u>H</u>$_2$), 2.83-2.93 (2H, m, C<u>H</u>$_2$), 4.57 (2H, s, C<u>H</u>$_2$), 4.64 (1H, q, J=6.6Hz, C<u>H</u>$_2$), 4.77 (2H, s, C<u>H</u>$_2$), 7.13-7.38 (8H, m, Ar-H), 7.44-7.51 (3H, m, Ar-H), 7.66 (1H, d, J=6.6Hz, Ar-H), 7.72 (1H, d, J=8.1Hz, Ar-H), 7.85 (1H, dd, J=2.4, 7.1Hz, Ar-H), 8.14 (1H, dd, J=2.2, 7.1Hz, Ar-H).

Example 102: Synthesis of K-2256

[0362] To 4-fluorobenzaldehyde (484.2 mg, 3.90 mmol) and 4-fluorobenzylamine (500 mg, 3.90 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.38 ml, 4.68 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (590.1 mg, 15.6 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 217 (783.2 mg, 84.0 %). MS m/z: 233.

[0363] The dibenzylamine compound 217 (500 mg, 2.15 mmol) and triethylamine (0.36 ml, 2.58 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (213.6 g, 2.36 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 218 (572.6 mg, 86.8 %). MS m/z: 287.

[0364] The conjugated ketone compound 218 (800 mg, 1.63 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (33.7 mg, 1.95 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2256 (375.1 mg, 48.2 %).

MS m/z: 458, ^{1}H-NMR δ: 1.50 (3H, d, J=6.6Hz, C<u>H</u>$_3$), 2.60 (2H, t, J=6.1Hz, C<u>H</u>$_2$), 2.84-2.96 (2H, m, C<u>H</u>$_2$), 4.36 (2H, s, C<u>H</u>$_2$), 4.54 (2H, s, C<u>H</u>$_2$), 4.66 (1H, q, J=6.6Hz, C<u>H</u>), 6.95-7.09 (6H, m, Ar-H), 7.16 (1H, d, J=8.8Hz, Ar-H), 7.17 (1H, d, J=8.8Hz, Ar-H), 7.43-7.51 (3H, m, Ar-H), 7.67 (1H, d, J=6.6Hz, Ar-H), 7.73 (1H, d, J=8.3Hz, Ar-H), 7.87 (1H, dd, J=2.4, 7.0Hz, Ar-H), 8.17 (1H, dd, J=2.0, 7.3Hz, Ar-H).

Example 103: Synthesis of K-2261

[0365] To 3-chlorobenzaldehyde (992.7 mg, 7.06 mmol) and 4-chlorobenzylamine (1 g, 7.06 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (2.5 ml, 8.47 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (1.0683 g, 28.4 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for

12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 219 (1.5847 g, 84.4 %). MS m/z: 266.

[0366] The dibenzylamine compound 219 (1.3 g, 4.89 mmol) and triethylamine (0.82 ml, 5.86 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (486.6 mg, 5.38 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 220 (1.2967 g, 82.7 %). MS m/z: 320.

[0367] The conjugated ketone compound 220 (1 g, 3.13 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (642.2 mg, 3.75 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2261 (624.8 mg, 40.7 %).

MS m/z: 491, ^{1}H-NMR δ: 1.50 (3H, d, J=6.6Hz, C<u>H</u>$_3$), 2.54-2.63 (2H, m, C<u>H</u>$_2$), 2.82-2.96 (2H, m, C<u>H</u>$_2$), 4.36 (2H, d, J=4.4Hz, C<u>H</u>$_2$), 4.55 (2H, d, J=2.9Hz, C<u>H</u>$_2$), 4.65 (1H, q, J=6.6Hz, C<u>H</u>), 7.04 (2H, d, J=8.6Hz, Ar-H), 7.13 (2H, d, J=8.6Hz, Ar-H), 7.18-7.31 (4H, m, Ar-H), 7.44-7.51 (3H, m, Ar-H), 7.67 (1H, d, J=7.3Hz, Ar-H), 7.73 (1H, d, J=8.1Hz, Ar-H), 7.85 (1H, dd, J=2.2Hz, J=7.3Hz, Ar-H), 8.16 (1H, d, J=7.6Hz, Ar-H).

Example 104: Synthesis of K-2262 (N1-(2-chlorobenzyl)-N1-(4-chlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0368] To 2-chlorobenzaldehyde (992.7 mg, 7.06 mmol) and 4-chlorobenzylamine (1 g, 7.06 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (2.5 ml, 8.47 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (1.0683 g, 28.4 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 221 (673.6 mg, 40 %). MS m/z: 266.

[0369] The dibenzylamine compound 221 (600 mg, 2.26 mmol) and triethylamine (0.38 ml, 2.71 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (224.6 mg, 2.48 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 222 (684.2 mg, 94.8 %). MS m/z: 320.

[0370] The conjugated ketone compound 222 (500 mg, 1.56 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (321.1 mg, 1.88 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2262 (552.4 mg, 72.0 %).

MS m/z: 491, ^{1}H-NMR δ: 1.56 (3H, d, J=6.6Hz, C<u>H</u>$_3$), 2.51-2.72 (2H, m, C<u>H</u>$_2$), 2.83-2.98 (2H, m, C<u>H</u>$_2$), 4.43 (1H, s, C<u>H</u>$_2$), 4.48 (1H, s, C<u>H</u>$_2$), 4.56 (1H, d, J=4.5Hz, C<u>H</u>$_2$), 4.68-4.72 (1H, m, C<u>H</u>), 4.73 (1H, d, J=5.6Hz, C<u>H</u>$_2$), 7.05 (1H, d, J=8.3Hz, Ar-H), 7.15 (1H, d, J=8.3Hz, Ar-H), 7.20-7.39 (6H, m, Ar-H), 7.45-7.52 (3H, m, Ar-H), 7.68 (1H, d, J=6.3Hz, Ar-H), 7.75 (1H, d, J=8.3Hz, Ar-H), 7.87 (1H, d, J=7.1Hz, Ar-H), 8.14 (1H, d, J=6.6Hz, Ar-H).

Example 105: Synthesis of K-2264 (N1-(3,4-dichlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]-amino}propanamide)

[0371] To 3,4-dichlorobenzaldehyde (1 g, 5.71 mmol) and 4-trifluoromethylbenzylamine (1 g, 5.71 mmol, 1.0 mol eq.)

was added titanium tetraisopropoxide (2.02 ml, 6.86 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (864.6 mg, 22.86 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 223 (1.668 g, 87.4 %).

MS m/z: 334, ^{1}H-NMR d: 3.75 (2H, s, C<u>H$_2$</u>), 3.84 (2H, s, C<u>H$_2$</u>), 7.17 (1H, dd, J=2.2, 8.3Hz, Ar-H), 7.39 (2H, d, 8.3Hz, Ar-H), 7.45 (1H, d, J=8.3Hz, Ar-H), 7.46 (1H, d, J=2.2Hz, Ar-H), 7.59 (2H, d, J=8.3Hz, Ar-H).

[0372] The dibenzylamine compound 223 (800 mg, 2.39 mmol) and triethylamine (0.4 ml, 2.87 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (238.4 mg, 2.63 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 224 (930 mg, 100.0 %).

MS m/z: 388, ^{1}H-NMR d: 4.54 (2H, d, J=42.0Hz, C<u>H$_2$</u>), 4.64 (2H, d, J=39.0Hz, C<u>H$_2$</u>), 5.79-5.82 (1H, m, CH=C<u>H$_2$</u>), 6.53-6.60 (2H, m, C<u>H</u>=C<u>H$_2$</u>), 7.23-7.45 (5H, m, Ar-H), 7.58 (1H, d, J=7.8Hz, Ar-H), 7.63 (1H, d, J=7.8Hz, Ar-H).

[0373] The conjugated ketone compound 224 (800 mg, 2.06 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (387.7 mg, 2.26 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2264 (807.4 mg, 70.1 %).

MS m/z: 559, ^{1}H-NMR d: 1.51 (3H, d, J=6.6Hz, C<u>H$_3$</u>), 2.59 (2H, t, J=6.1Hz, C<u>H$_2$</u>), 2.85-2.98 (2H, m, C<u>H$_2$</u>), 4.41 (2H, d, J=42.0Hz, C<u>H$_2$</u>), 4.58 (2H, d, J=38.1Hz, C<u>H$_2$</u>), 4.66 (1H, q, J=6.6Hz, C<u>H</u>), 7.19 (1H, d, J=2.0Hz, Ar-H), 7.22 (1H, d, J=8.3Hz, Ar-H), 7.30 (2H, d, J=8.3Hz, Ar-H), 7.44-7.52 (3H, m, Ar-H), 7.55 (1H, d, J=8.3Hz, Ar-H), 7.59 (1H, d, J=8.3Hz, Ar-H), 7.66 (1H, d, J=7.1Hz, Ar-H), 7.74 (1H, d, J=8.3Hz, Ar-H), 7.86 (1H, dd, J=2.9, 6.6Hz, Ar-H), 8.17 (1H, d, J=8.3Hz, Ar-H).

Example 106: Synthesis of K-2265 (N1,N1-di(3,4-dichlorobenzyl)-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0374] To 3,4-dichlorobenzaldehyde (500 mg, 2.86 mmol) and 3,4-dichlorobenzylamine (0.382 ml, 2.86 mmol) was added titanium tetraisopropoxide (1.51 ml, 5.14 mmol, 1.8 mol eq.) and the mixture was stirred at room temperature for 28 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (443 mg, 11.44 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 20 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added chloroform and water and the mixture was filtered through celite. The residue was washed with chloroform and the washing liquor was combined with the filtrate and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane: ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 225 (712.2 mg, 74.3 %).

MS m/z: 335, ^{1}H-NMR d: 3.74 (4H, d, J=2.7, C<u>H$_2$</u>×2), 7.17 (2H, dd, J=2.0, 8.3Hz, Ar-H), 7.39 (2H, d, J=8.3Hz, Ar-H), 7.44 (2H, d, J=2.0Hz, Ar-H).

[0375] The dibenzylamine compound 225 (315 mg, 0.94 mmol) and triethylamine (0.16 ml, 1.13 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (94 mg, 1.04 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil

226 (347.1 mg, 94.9 %).

MS m/z: 389, ^{1}H-NMR d: 4.47 (2H, s, C$\underline{H}_2$), 4.58 (2H, s, C$\underline{H}_2$), 5.58 (1H, dd, J=5.9, 6.6Hz, CH=C$\underline{H}_2$), 6.52 (1H, d, J=5.9Hz, C$\underline{H}$=CH$_2$), 6.52 (1H, d, J=6.6Hz, CH=C$\underline{H}_2$), 6.99 (1H, d, J=7.6Hz, Ar-H), 7.08 (1H, d, J=7.6Hz, Ar-H), 7.23 (1H, s, Ar-H), 7.32 (1H, s, Ar-H), 7.39 (1H, d, J=7.8Hz, Ar-H), 7.44 (1H, d, J=7.3Hz, Ar-H).

[0376] The conjugated ketone compound 226 (280 mg, 0.72 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (148 mg, 0.864 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 8 days. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2265 (314.1 mg, 77.9 %). Subsequently, the obtained K-2265 (201.7 mg, 0.36 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 10 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallized from ethanol/water to thereby give K-2265 hydrochloride (188.2 mg, 87.6 %) as colorless crystals.

MS m/z: 560, ^{1}H-NMR d: 1.56 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.55-2.63 (2H, m, C$\underline{H}_2$), 2.86-2.99 (2H, m, C$\underline{H}_2$), 4.35 (2H, s, C$\underline{H}_2$), 4.51 (2H, s, C$\underline{H}_2$), 4.71 (1H, q, J=6.6Hz, C$\underline{H}$), 6.94 (1H, dd, J=2.2, 8.3Hz, Ar-H), 7.04 (1H, dd, J=2.2, 8.1Hz, Ar-H), 7.18 (1H, d, J=2.0Hz, Ar-H), 7.27 (1H, d, J=2.0Hz, Ar-H), 7.37 (1H, d, J=8.1Hz, Ar-H), 7.40 (1H, d, J=8.3Hz, Ar-H), 7.45-7.52 (3H, m, Ar-H), 7.68 (1H, d, J=6.6Hz, Ar-H), 7.75 (1H, d, J=8.1Hz, Ar-H), 7.87 (1H, dd, J=2.2, 7.3Hz, Ar-H), 8.15 (1H, d, J=7.3Hz, Ar-H).

Example 107: Synthesis of K-2266 (N1-(4-chlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0377] To 4-(trifluoromethyl)benzaldehyde (1 g, 5.74 mmol) and 4-chlorobenzylamine (813.2 mg, 5.74 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (2.03 ml, 6.89 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (868.6 mg, 22.96 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 227 (1.6267 g, 94.5 %).

MS m/z: 299, ^{1}H-NMR d: 3.77 (2H, s, C$\underline{H}_2$), 3.84 (2H, s, C$\underline{H}_2$), 7.27 (2H, d, J=9.0Hz, Ar-H), 7.30 (2H, d, J=9.0Hz, Ar-H), 7.46 (2H, d, J=8.1Hz, Ar-H), 7.58 (2H, d, J=8.1Hz, Ar-H).

[0378] The dibenzylamine compound 227 (800 mg, 2.67 mmol) and triethylamine (0.45 ml, 3.20 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (265.7 mg, 2.94 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 228 (938.5 mg, 99.3 %).

MS m/z: 353, ^{1}H-NMR d: 4.53 (2H, d, J=26.8Hz, C$\underline{H}_2$), 4.65 (2H, d, J=24.4Hz, C$\underline{H}_2$), 5.79 (1H, dd, J=2.4, 9.8Hz, CH=C$\underline{H}_2$), 6.50 (1H, dd, J=2.4, 16.6Hz, C$\underline{H}$=CH$_2$), 6.59 (1H, dd, J=9.8, 16.6Hz, CH=C$\underline{H}_2$), 7.10 (1H, d, J=8.3Hz, Ar-H), 7.19 (1H, d, J=8.3Hz, Ar-H), 7.27 (1H, d, J=8.3Hz, Ar-H), 7.29 (1H, d, J=8.3Hz, Ar-H), 7.34 (1H, d, J=7.8Hz, Ar-H), 7.36 (1H, d, J=6.8Hz, Ar-H), 7.57 (1H, d, J=7.8Hz, Ar-H), 7.62 (1H, d, J=7.8Hz, Ar-H).

[0379] The conjugated ketone compound 228 (800 mg, 2.26 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (425.4 mg, 2.48 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2266 (981.5 mg, 82.8 %).

MS m/z: 524, ^{1}H-NMR d: 1.52 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.57-2.64 (2H, m, C$\underline{H}_2$), 2.84-2.97 (2H, m, C$\underline{H}_2$), 4.41 (2H,

d, J=23.9Hz, CH_2), 4.59 (2H, d, J=24.9Hz, CH_2), 4.67 (1H, q, J=6.6Hz, CH), 7.04 (1H, d, J=8.3Hz, Ar-H), 7.13 (1H, d, J=8.3Hz, Ar-H), 7.21 (1H, d, J=8.3Hz, Ar-H), 7.26-7.31 (3H, m, Ar-H), 7.44-7.51 (3H, m, Ar-H), 7.55 (1H, d, J=8.1Hz, Ar-H), 7.59 (1H, d, J=8.1Hz, Ar-H), 7.67 (1H, dd, J=3.0, 6.6Hz, Ar-H), 7.74 (1H, d, J=8.1Hz, Ar-H), 7.87 (1H, dd, J=2.0, 8.1Hz, Ar-H), 8.17 (1H, d, J=8.1Hz, Ar-H).

Example 108: Synthesis of K-2267 (N1-(4-chlorobenzyl)-N1-(3,4-dichlorobenzyl)-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0380] 4-Chlorobenzylamine (1 g, 7.06 mmol) and 3,4-dichloro-benzaldehyde (1.36 g, 7.77 mmol, 1.1 mol eq.) were dissolved in methanol and $MgSO_4$ (1.02 g, 8.47 mmol, 1.2 mol eq.) and AcOH (10 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 2 hours. After the completion of the reaction, sodium boron hydride (334.0 mg, 8.83 mmol, 1.25 mol eq.) was added under ice-cooling to the reaction mixture. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 229 (1.6777 g, 79.2 %).

MS m/z: 279, ^{1}H-NMR d: 3.72 (2H, s, CH_2), 3.73 (2H, s, CH_2), 7.15 (1H, dd, J=2.0, 8.1Hz, Ar-H), 7.24 (2H, d, J=8.8Hz, Ar-H), 7.29 (2H, d, J=8.8Hz, Ar-H), 7.38 (1H, d, J=8.1Hz, Ar-H), 7.43 (1H, d, J=2.0Hz, Ar-H).

[0381] The dibenzylamine compound 229 (800 mg, 2.66 mmol) and triethylamine (0.45 ml, 3.19 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (265 mg, 2.93 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 230 (768.9 mg, 81.4 %).

MS m/z: 333, ^{1}H-NMR d: 4.47 (2H, d, J=13.4Hz, CH_2), 4.57 (2H, d, J=13.9Hz, CH_2), 5.79 (1H, dd, J=3.2, 9.0Hz, CH=CH_2), 6.50 (1H, dd, J=3.2, 16.6Hz, CH=CH_2), 6.57 (1H, dd, J=9.0, 16.6Hz, CH=CH_2), 7.08-7.46 (7H, m, Ar-H).

[0382] The conjugated ketone compound 230 (600 mg, 1.69 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (347.2 mg, 2.03 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2267 (721.3 mg, 81.1 %).

MS m/z: 504, ^{1}H-NMR d: 1.51 (3H, d, J=6.6Hz, CH_3), 2.55-2.62 (2H, m, CH_2), 2.84-2.97 (2H, m, CH_2), 4.35 (2H, d, J=18.3Hz, CH_2), 4.52 (2H, d, J=12.9Hz, CH_2), 4.66 (1H, q, J=6.6Hz, CH), 7.04 (2H, d, J=8.3Hz, Ar-H), 7.13 (1H, d, J=8.3Hz, Ar-H), 7.27-7.29 (1H, m, Ar-H), 7.31 (1H, d, J=8.3Hz, Ar-H), 7.36 (1H, d, J=8.1Hz, Ar-H), 7.39 (1H, d, J=8.1Hz, Ar-H), 7.45-7.50 (3H, m, Ar-H), 7.66 (1H, d, J=7.1Hz, Ar-H), 7.74 (1H, d, J=8.3Hz, Ar-H), 7.87 (1H, dd, J=2.2, 8.3Hz, Ar-H), 8.17 (1H, d, J=7.1Hz, Ar-H).

Example 109: Synthesis of K-2270 (N1,N1-di(4-methoxybenzyl)-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0383] To 4-anisaldehyde (0.447 ml, 3.67 mmol) and 4-methoxybenzylamine (0.479 ml, 3.67 mmol, 1.0 mol eq.) was added titanium tetraisopropoxide (1.30 ml, 4.40 mmol, 1.2 mol eq.) and the mixture was stirred at room temperature for 10 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (555 mg, 14.68 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 231 (762.7 mg, 80.9 %).

MS m/z: 257, ^{1}H-NMR d: 3.73 (4H, s, CH_2), 3.80 (6H, s, OCH_3), 6.86 (4H, d, J=8.5Hz, Ar-H), 7.25 (4H, d, J=8.5Hz,

Ar-H).

[0384] The dibenzylamine compound 231 (500 mg, 1.95 mmol) and triethylamine (0.33 ml, 2.33 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (195 mg, 2.15 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 232 (602.8 mg, 99.4 %).

MS m/z: 311, ^{1}H-NMR d: 3.80 (3H, s, OC$\underline{H}_3$), 3.81 (3H, s, OC$\underline{H}_3$), 4.43 (2H, s, C$\underline{H}_2$), 4.56 (2H, s, C$\underline{H}_2$), 5.73 (1H, dd, J=2.2, 10.2Hz, CH=C$\underline{H}_2$), 6.48 (1H, dd, J=2.2, 16.6Hz, C$\underline{H}$=CH$_2$), 6.62 (1H, dd, J=10.2, 16.6Hz, CH=C$\underline{H}_2$), 6.85 (2H, d, J=8.5Hz, Ar-H), 6.88 (3H, d, J=8.5Hz, Ar-H), 7.08 (2H, d, J=8.5Hz, Ar-H), 7.19 (1H, d, J=8.5Hz, Ar-H).

[0385] The conjugated ketone compound 232 (450 mg, 1.45 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (297 mg, 1.74 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 2 weeks. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2270 (366.9 mg, 52.5 %). Subsequently, the obtained K-2270 (244.5 mg, 0.51 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 10 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallised from ethanol/water to thereby give K-2270 hydrochloride (150.7 mg, 57.3 %) as colorless crystals.

MS m/z: 482, ^{1}H-NMR d: 1.58 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.63-2.75 (2H, m, C$\underline{H}_2$), 2.86-2.98 (2H, m, C$\underline{H}_2$), 3.79 (3H, s, OC$\underline{H}_3$), 3.80 (3H, s, OC$\underline{H}_3$), 4.32 (2H, s, C$\underline{H}_2$), 4.48 (1H, d, J=14.5Hz, C$\underline{H}_2$), 4.55 (1H, d, J=14.5Hz, C$\underline{H}_2$), 4.75 (1H, q, J=6.6Hz, C$\underline{H}$), 6.83 (2H, d, J=8.8Hz, Ar-H), 6.86 (2H, d, J=8.6Hz, Ar-H), 7.03 (2H, d, J=8.5Hz, Ar-H), 7.14 (2H, d, J=8.5Hz, Ar-H), 7.46-7.53 (3H, m, Ar-H), 7.74 (1H, d, J=7.8Hz, Ar-H), 7.76 (1H, d, J=8.8Hz, Ar-H), 7.88 (1H, d, J=7.6Hz, Ar-H), 8.15 (1H, d, J=8.1Hz, Ar-H).

Example 110: Synthesis of K-2272 (N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]-amino}propanamide)

[0386] 3,4-Dichlorobenzylamine (0.379 ml, 2.84 mmol) and 4-(trifluoromethoxy)benzaldehyde (503.6 mg, 3.56 mmol, 1.0 mol eq.) were dissolved in methanol and $MgSO_4$ (410.2 mg, 3.41 mmol, 1.2 mol eq.) and AcOH (3 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, sodium boron hydride (134 mg, 3.55 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 10 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane : ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 233 (777.3 mg, 78.2 %).

MS m/z: 350, ^{1}H-NMR d: 3.76 (2H, s, C$\underline{H}_2$), 3.79 (2H, s, C$\underline{H}_2$), 7.18 (1H, dd, J=2.0, 8.5Hz, Ar-H), 7.18 (2H, d, J=8.5Hz, Ar-H), 7.36 (2H, d, J=8.5Hz, Ar-H), 7.39 (1H, d, J=8.5Hz, Ar-H), 7.46 (1H, d, J=2.0Hz, Ar-H).

[0387] The dibenzylamine compound 233 (500 mg, 1.43 mmol) and triethylamine (0.238 ml, 1.71 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (142 mg, 1.57 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 234 (454.6 mg, 78.7 %).

MS m/z: 404, ^{1}H-NMR d: 4.50 (2H, d, J=19.0Hz, C$\underline{H}_2$), 4.61 (2H, d, J=21.7Hz, C$\underline{H}_2$), 5.80 (1H, dd, J=1.7, 9.5Hz, CH=C$\underline{H}_2$), 6.53 (1H, d, J=1.7, 16.6Hz, C$\underline{H}$=CH$_2$), 6.58 (1H, d, J=9.5, 16.6Hz, CH=C$\underline{H}_2$), 7.16-7.22 (5H, m, Ar-H), 7.32 (1H, s, Ar-H), 7.41 (1H, d, J=8.3Hz, Ar-H).

[0388] The conjugated ketone compound 234 (350 mg, 0.87 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (178 mg, 1.04 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2272 (360.7 mg, 72.4 %). Subsequently, the obtained K-2272 (250 mg, 0.435 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 10 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallised from ethanol/water to thereby give K-2270 hydrochloride (230.2 mg, 86.5 %) as colorless crystals.

MS m/z: 575, ^{1}H-NMR d: 1.60 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.60-2.76 (2H, m, C$\underline{H}_2$), 2.88-3.02 (2M, m, C$\underline{H}_2$), 4.37 (2H, d, J=22.7Hz, C$\underline{H}_2$), 4.51 (1H, d, J=2.4Hz C$\underline{H}_2$), 4.57 (1H, d, J=6.1Hz, C$\underline{H}_2$), 4.72-4.82 (1H, m, C$\underline{H}$), 7.13 (1H, d, J=8.8Hz, Ar-H), 7.15 (1H, d, J=7.3Hz, Ar-H), 7.17 (1H, d, J=6.8Hz, Ar-H), 7.19 (1H, d, J=8.8Hz, Ar-H), 7.22 (1H, d, J=8.8Hz, Ar-H), 7.28 (1H, d, J=2.0Hz, Ar-H), 7.37 (1H, d, J=8.3Hz, Ar-H), 7.38 (1H, dd, J=8.3, 9.3Hz, Ar-H), 7.47-7.55 (3H, m, Ar-H), 7.72 (1H, d, J=7.1Hz, Ar-H), 7.77 (1H, d, J=8.1Hz, Ar-H), 7.88 (1H, dd, J=2.0, 7.8Hz, Ar-H), 8.14 (1H, d, J=7.8Hz, Ar-H).

Example 111: Synthesis of K-2283 (N1-(4-chlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]-amino}propanamide)

[0389] 4-(Trifluoromethoxy)benzaldehyde (0.555 ml, 3.88 mmol, 1.1 mol eq.) and 4-chlorobenzylamine (0.430 ml, 3.53 mmol) were dissolved in methanol and $MgSO_4$ (509.89 mg, 4.24 mmol, 1.2 mol eq.) and AcOH (3 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 10 minutes. After the completion of the reaction, sodium boron hydride (167 mg, 4.41 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 10 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane : ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 235 (1.092 g, 98.1 %).

MS m/z: 315, ^{1}H-NMR d: 3.77 (2H, s, C$\underline{H}_2$), 3.79 (2H, s, C$\underline{H}_2$), 7.18 (2H, d, J=7.8Hz, Ar-H), 7.29 (4H, d, J=2.2Hz, Ar-H), 7.37 (2H, d, J=8.9Hz, Ar-H).

[0390] The dibenzylamine compound 235 (500 mg, 1.58 mmol) and triethylamine (0.265 ml, 1.90 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (158 mg, 1.74 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 40 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 236 (521.3 mg, 89.3 %).

MS m/z: 369, ^{1}H-NMR d: 4.50 (2H, d, J=4.9Hz, C$\underline{H}_2$), 4.61 (2H, d, J=8.1Hz, C$\underline{H}_2$), 5.78 (1H, dd, J=2.7, 9.5Hz, CH=C$\underline{H}_2$), 6.50 (1H, dd, J=2.7, 16.6Hz, C$\underline{H}$=CH$_2$), 6.57 (1H, dd, J=9.5, 16.6Hz, CH=C$\underline{H}_2$), 7.09 (1H, d, J=8.3Hz, Ar-H), 7.15-7.21 (4H, m, Ar-H), 7.27 (1H, d, J=8.1Hz, Ar-H), 7.28 (1H, d, J=8.1Hz, Ar-H), 7.33 (1H, d, J=8.1Hz, Ar-H).

[0391] The conjugated ketone compound 236 (400 mg, 1.08 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (222 mg, 1.30 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 8 days. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2283 (452.0 mg, 77.4 %). Subsequently, the obtained K-2283 (248.9 mg, 0.46 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 15 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were washed with diethyl ether to thereby give K-2283 hydrochloride (235.0 mg, 88.5 %) as colorless crystals.

MS m/z: 540, ^{1}H-NMR d: 1.60 (3H, d, J=6.3Hz, C$\underline{H}_3$), 2.62-2.74 (2H, m, C$\underline{H}_2$), 2.87-2.99 (2H, m, C$\underline{H}_2$), 4.38 (2H, d, J=4.9Hz, C$\underline{H}_2$), 4.55 (2H, t, J=8.3Hz, C$\underline{H}_2$), 4.75-4.80 (1H, m, C$\underline{H}$), 7.04 (1H, d, J=8.5Hz, Ar-H), 7.12 (2H, d, J=8.5Hz, Ar-H), 7.14 (1H, d, J=8.5Hz, Ar-H), 7.22 (1H, d, J=8.5Hz, Ar-H), 7.27 (2H, d, J=8.5Hz, Ar-H), 7.30 (1H, d, J=8.5Hz, Ar-H), 7.45-7.53 (3H, m, Ar-H), 7.72 (1H, d, J=7.1Hz, Ar-H), 7.77 (1H, d, J=8.1Hz, Ar-H), 7.88 (1H, dd,

J=2.0, 7.3Hz, Ar-H), 8.14 (1H, d, J=7.8Hz, Ar-H).

Example 112: Synthesis of K-2289 (N1-(4-chlorobenzyl)-N1-(4-methoxybenzyl)-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0392] 4-Chlorobenzaldehyde (564 mg, 4.01 mmol, 1.1 mol eq.) and 4-methoxybenzylamine (476 mg, 3.64 mmol) were dissolved in methanol and $MgSO_4$ (525.8 mg, 4.37 mmol, 1.2 mol eq.) and AcOH (5 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 40 minutes. After the completion of the reaction, sodium boron hydride (172 mg, 4.55 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 15 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane : ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 237 (711.8 mg, 74.8 %).

MS m/z: 261, ^{1}H-NMR d: 3.72 (2H, s, $C\underline{H}_2$), 3.75 (2H, s, $C\underline{H}_2$), 3.80 (3H, s, $OC\underline{H}_3$), 6.86 (2H, d, J=8.5Hz, Ar-H), 7.24 (2H, d, J=8.5Hz, Ar-H), 7.28 (4H, d, J=2.2Hz, Ar-H).

[0393] The dibenzylamine compound 237 (501.4 mg, 1.92 mmol) and triethylamine (0.32 ml, 2.30 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (191 mg, 2.11 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 238 (557.2 mg, 91.9 %).

MS m/z: 315, ^{1}H-NMR d: 3.80 (3H, d, J=5.4Hz, $OC\underline{H}_3$), 4.44 (2H, d, J=8.5Hz, $C\underline{H}_2$), 4.57 (2H, d, J=4.1Hz, $C\underline{H}_2$), 5.75 (1H, dd, J=1.7, 10.3Hz, $CH=C\underline{H}_2$), 6.48 (1H, dd, J=1.7, 16.6Hz, $C\underline{H}=CH_2$), 6.64 (1H, dd, J=10.3, 16.6Hz, $CH=C\underline{H}_2$), 6.85 (1H, d, J=8.3Hz, Ar-H), 6.88 (1H, d, J=8.5Hz, Ar-H), 7.07 (1H, d, J=8.3Hz, Ar-H), 7.08 (1H, d, J=6.3Hz, Ar-H), 7.17 (1H, d, J=8.8Hz, Ar-H), 7.19 (1H, d, J=8.3Hz, Ar-H), 7.28 (1H, d, J=8.5Hz, Ar-H), 7.32 (2H, d, J=7.8Hz, Ar-H).

[0394] The conjugated ketone compound 238 (414 mg, 1.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (270 mg, 1.57 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 12 days. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2289 (441.8 mg, 69.3 %). Subsequently, the obtained K-2289 (269.4 mg, 0.55 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 10 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallized from ethanol/water to thereby give K-2289 hydrochloride (270.1 mg, 93.2 %) as colorless crystals.

MS m/z: 486, ^{1}H-NMR d: 1.56 (3H, d, J=6.6Hz, $C\underline{H}_3$), 2.57-2.70 (2H, m, $C\underline{H}_2$), 2.84-2.95 (2H, m, $C\underline{H}_2$), 3.80 (3H, d, J=2.2Hz, $OC\underline{H}_3$), 4.33 (2H, d, J=5.4Hz, $C\underline{H}_2$), 4.52 (2H, t, J=6.6Hz, $C\underline{H}_2$), 4.70-4.74 (1H, m, $C\underline{H}$), 6.83 (1H, d, J=9.0Hz, Ar-H), 6.85 (1H, d, J=9.0Hz, Ar-H), 7.02 (1H, d, J=8.5Hz, Ar-H), 7.03 (1H, d, J=8.5Hz, Ar-H), 7.12 (1H, d, J=8.5Hz, Ar-H), 7.13 (1H, d, J=8.3Hz, Ar-H), 7.27 (1H, d, J=8.5Hz, Ar-H), 7.29 (1H, d, J=8.5Hz, Ar-H), 7.46-7.52 (3H, m, Ar-H), 7.71 (1H, dd, J=3.4, 6.8Hz, Ar-H), 7.75 (1H, d, J=8.3Hz, Ar-H), 7.87 (1H, d, J=7.6Hz, Ar-H), 8.15 (1H, d, J=7.6Hz, Ar-H).

Example 113: Synthesis of K-2290 (N1-(4-methoxybenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0395] 4-(Trifluoromethyl)benzaldehyde (1.269 g, 7.29 mmol) and 4-methoxybenzylamine (1 g, 7.29 mmol, 1.0 mol eq.) were dissolved in methanol and $MgSO_4$ (1.0530 g, 8.75 mmol, 1.2 mol eq.) and AcOH (10 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was dissolved in methanol and sodium boron hydride (344.7 mg, 9.11 mmol, 1.25 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl

acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 239 (1.40 g, 65.0 %).

MS m/z: 295, ^{1}H-NMR d: 3.73 (2H, s, CH_2), 3.80 (3H, s, OCH_3), 3.83 (2H, s, CH_2), 6.87 (2H, d, J=8.5Hz, Ar-H), 7.24 (2H, d, J=8.5Hz, Ar-H), 7.45 (2H, d, J=8.5Hz, Ar-H), 7.57 (1H, d, J=8.5Hz, Ar-H), 7.59 (1H, d, J=8.5Hz, Ar-H).

[0396] The dibenzylamine compound 239 (1.30 g, 4.40 mmol) and triethylamine (0.74 ml, 5.28 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (438.3 mg, 4.84 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 240 (974.7 mg, 63.5 %).

MS m/z: 349, ^{1}H-NMR d: 3.80 (3H, d, J=4.9Hz, OCH_3), 4.53 (2H, d, J=52.0Hz, CH_2), 4.61 (2H, d, J=45.1Hz, CH_2), 5.77 (1H, dd, J=2.0, 10.5Hz, $CH=CH_2$), 6.49 (1H, dd, J=2.0, 16.6Hz, $CH=CH_2$), 6.65 (1H, dd, J=10.5, 16.6Hz, $CH=CH_2$), 6.85 (1H, d, J=8.3Hz, Ar-H), 6.89 (1H, d, J=8.5Hz, Ar-H), 7.07 (1H, d, J=8.3Hz, Ar-H), 7.17 (1H, d, J=8.1Hz, Ar-H), 7.27 (1H, d, J=6.8Hz, Ar-H), 7.35 (1H, d, J=7.8Hz, Ar-H), 7.56 (1H, d, J=8.1Hz, Ar-H), 7.61 (1H, d, J=7.3Hz, Ar-H).

[0397] The conjugated ketone compound 240 (874.7 mg, 2.50 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (513.9 mg, 3.00 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2290 (1.005 g, 77.2 %).

MS m/z: 520, ^{1}H-NMR d: 1.51 (3H, dd, J=3.0, 6.6Hz, CH_3), 2.55 (1H, t, J=6.1Hz, CH_2), 2.67 (1H, t, J=6.1Hz, CH_2), 2.82-2.98 (2H, m, CH_2), 3.79 (3H, d, J=4.6Hz, OCH_3), 4.39 (2H, d, J=28.3Hz, CH_2), 4.57 (2H, d, J=30.0Hz, CH_2), 4.64-4.70 (1H, m, CH), 6.83 (1H, d, J=8.8Hz, Ar-H), 6.86 (1H, d, J=8.8Hz, Ar-H), 7.03 (1H, d, J=8.8Hz, Ar-H), 7.12 (1H, d, J=8.6Hz, Ar-H), 7.21 (1H, d, J=8.1Hz, Ar-H), 7.30 (1H, d, J=8.3Hz, Ar-H), 7.43-7.51 (3H, m, Ar-H), 7.54 (1H, d, J=8.3Hz, Ar-H), 7.57 (1H, d, J=8.1Hz, Ar-H, 7.68 (1H, t, J=7.6Hz, Ar-H), 7.73 (1H, dd, J=3.7, 8.1Hz, Ar-H), 7.86 (1H, dd, J=2.4, 7.3Hz, Ar-H), 8.17 (1H, d, J=7.6Hz, Ar-H).

Example 114: Synthesis of K-2291 (N1-(4-chlorobenzyl)-N1-(2-naphthylmethyl)-3-[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide)

[0398] To 2-naphthaldehyde (500 mg, 3.20 mmol) and 4-chlorobenzylamine (0.389 ml, 3.20 mmol, 1.0 mol eq.) was added titanium isopropoxide (1.70 ml, 5.76 mmol, 1.8 mol eq.) and the obtained mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was dissolved in ethanol and sodium boron hydride (485 mg, 12.82 mmol, 4.0 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 29 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 241 (767.4 mg, 85.2 %).

MS m/z: 281, ^{1}H-NMR d: 3.80 (2H, s, CH_2), 3.95 (2H, s, CH_2), 7.26 (2H, d, J=12.0Hz, Ar-H), 7.31 (2H, d, J=12.0Hz, Ar-H), 7.42-7.49 (3H, m, Ar-H), 7.75 (1H, s, Ar-H), 7.81 (1H, d, J=8.1Hz, Ar-H), 7.82 (1H, d, J=8.5Hz, Ar-H), 7.83 (1H, d, J=8.1Hz, Ar-H).

[0399] The dibenzylamine compound 241 (506.7 mg, 1.80 mmol) and triethylamine (0.301 ml, 2.16 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (179 mg, 1.98 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After dis-

tilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 242 (652.4 mg, 100 %).

MS m/z: 335, ^{1}H-NMR d: 4.58 (2H, d, J=65.9Hz, C$\underline{H}_2$), 4.74 (2H, d, J=52.0Hz, C$\underline{H}_2$), 5.76 (1H, dd, J=2.0, 10.2Hz, CH=C$\underline{H}_2$), 6.53 (1H, dd, J=2.0, 16.6Hz, C$\underline{H}$=CH$_2$), 6.54 (1H, dd, J=10.2, 16.6Hz, CH=C$\underline{H}_2$), 7.10 (1H, d, J=8.1Hz, Ar-H), 7.21-7.35 (4H, m, Ar-H), 7.47-7.62 (3H, m, Ar-H), 7.79-7.86 (3H, m, Ar-H).

[0400] The conjugated ketone compound 242 (500 mg, 1.49 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (307 mg, 1.79 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 13 days. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2291 (521.1 g, 69.0 %). Subsequently, the obtained K-2291 (394.1 mg, 0.78 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 15 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallized from ethanol/water to thereby give K-2291 hydrochloride (358.7 mg, 85.1 %) as colorless crystals.

MS m/z: 506, ^{1}H-NMR d: 1.56 (3H, d, J=6.8Hz, C$\underline{H}_3$), 2.61-2.76 (2H, m, C$\underline{H}_2$), 2.88-3.01 (2H, m, C$\underline{H}_2$), 4.38 (1H, s, C$\underline{H}_2$), 4.55 (1H, s, C$\underline{H}_2$), 4.62 (1H, d, J=3.7Hz, C$\underline{H}_2$), 4.75 (1H, d, J=6.8Hz, C$\underline{H}_2$),, 4.70-4.76 (1H, m, C$\underline{H}$), 7.05 (1H, d, J=8.5Hz, Ar-H), 7.16 (1H, d, J=8.3Hz, Ar-H), 7.28 (1H, d, J=8.5Hz, Ar-H), 7.30 (1H, d, J=8.5Hz, Ar-H), 7.44-7.58 (6H, m, Ar-H), 7.69-7.89 (7H, m, Ar-H), 8.10-8.17 (1H, m, Ar-H).

Example 115: Synthesis of K-2294 (N1-(3,4-dichlorobenzyl)-N1-(4-methylbenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0401] 3,4-Dichlorobenzaldehyde (1.555 g, 8.25 mmol) and 4-methylbenzylamine (1 g, 8.25 mmol, 1.0 mol eq.) were dissolved in methanol and $MgSO_4$ (1.1920 g, 9.90 mmol, 1.2 mol eq.) and AcOH (10 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was dissolved in methanol and sodium boron hydride (390.2 mg, 10.30 mmol, 1.25 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 243 (1.5942 g, 69.2 %).

MS m/z: 280, ^{1}H-NMR d: 2.34 (3H, s, C$\underline{H}_3$), 3.73 (4H, s, C$\underline{H}_2$x2), 7.14 (2H, d, J=8.1Hz, Ar-H), 7.16 (1H, dd, J=2.0, 8.1Hz, Ar-H), 7.19 (2H, d, J=8.1Hz, Ar-H), 7.37 (1H, d, J=8.1Hz, Ar-H), 7.43 (1H, d, J=2.0Hz, Ar-H).

[0402] The dibenzylamine compound 243 (1.4942 g, 5.35 mmol) and triethylamine (0.89 ml, 6.42 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (532.6 mg, 5.88 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 244 (1.6587 g, 92.9 %).

MS m/z: 334, ^{1}H-NMR d: 2.34 (3H, d, J=6.3Hz, C$\underline{H}_3$), 4.46 (2H, d, J=13.4Hz, C$\underline{H}_2$), 4.58 (2H, d, J=16.1Hz, C$\underline{H}_2$), 5.76 (1H, dd, J=2.0, 10.2Hz, CH=C$\underline{H}_2$), 6.48 (1H, dd, J=2.0, 16.8Hz, C$\underline{H}$=CH$_2$), 6.63 (1H, dd, J=10.2, 16.8Hz, CH=C$\underline{H}_2$), 7.04 (2H, d, J=7.8Hz, Ar-H), 7.09 (1H, d, J=8.3Hz, Ar-H), 7.17 (2H, d, J=7.8Hz, Ar-H), 7.31 (1H, s, Ar-H), 7.37 (1H, d, J=8.3Hz, Ar-H).

[0403] The conjugated ketone compound 244 (1.5587 g, 4.67 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (959.6 mg, 5.60 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2294 (2.1115 g, 89.3 %).

MS m/z: 505, ^{1}H-NMR d: 1.50 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.34 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.52 (1H, dt, J=3.4, 9.3Hz, C$\underline{H}_2$), 2.63 (1H, t, J=6.3Hz, C$\underline{H}_2$), 2.74-2.96 (2H, m, C$\underline{H}_2$), 4.35 (2H, d, J=22.0Hz, C$\underline{H}_2$), 4.53 (2H, d, J=13.7Hz, C$\underline{H}_2$),

4.62-4.68 (1H m CH), 6.99 (1H, d, J=7.8Hz, Ar-H), 7.04 (1H, dd, J=2.0, 8.1Hz, Ar-H), 7.09 (1H, d, J=8.3Hz, Ar-H), 7.12 (1H, d, J=8.1Hz, Ar-H), 7.14 (1H, d, J=8.1Hz, Ar-H), 7.26 (1H, d, J=2.0Hz, Ar-H), 7.34 (1H, d, J=8.3Hz, Ar-H), 7.43-7.52 (3H, m, Ar-H), 7.68 (1H, d, J=7.1Hz, Ar-H), 7.72 (1H, d, J=8.1Hz, Ar-H), 7.85 (1H, d, J=7.1Hz, Ar-H), 8.17 (1H, d, J=7.1Hz, Ar-H).

Example 116: Synthesis of K-2299 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0404] 4-(Trifluoromethyl)benzaldehyde (1.4369 g, 8.25 mmol) and 4-methylbenzylamine (1 g, 8.25 mmol, 1.0 mol eq.) were dissolved in methanol and $MgSO_4$ (1.1920 g, 9.90 mmol, 1.2 mol eq.) and AcOH (10 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was dissolved in methanol and sodium boron hydride (390.2 mg, 10.30 mmol, 1.25 mol eq.) was added thereto. Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 245 (1.6877 g, 73.2 %).

MS m/z: 279, ^{1}H-NMR d: 2.34 (3H, s, CH_3), 3.76 (2H, s, CH_2), 3.85 (2H, s, CH_2), 7.14 (2H, d, J=7.8Hz, Ar-H), 7.21 (2H, d, J=8.1Hz, Ar-H), 7.46 (2H, d, J=8.1Hz, Ar-H), 7.57 (2H, d, J=8.3Hz, Ar-H).

[0405] The dibenzylamine compound 245 (1.5877 g, 5.68 mmol) and triethylamine (0.95 ml, 6.82 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (565.96 mg, 6.25 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 246 (1.5568 g, 82.0 %).

MS m/z: 333, ^{1}H-NMR d: 2.34 (3H, d, J=6.8Hz, CH_3), 4.52 (2H, d, J=26.8Hz, CH_2), 4.65 (2H, d, J=22.4Hz, CH_2), 5.76 (1H, dd, J=1.7, 10.2Hz, CH=CH_2), 6.49 (1H, dd, J=1.7, 16.8Hz, CH=CH_2), 6.64 (1H, dd, J=10.2, 16.8Hz, CH=CH_2), 7.05 (2H, d, J=7.8Hz, Ar-H), 7.17 (2H d, J=7.8Hz, Ar-H), 7.35 (2H, d, J=8.1Hz, Ar-H), 7.56 (2H, d, J=8.1Hz, Ar-H).

[0406] The conjugated ketone compound 246 (1.4568 g, 4.36 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (896.8 mg, 5.24 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 1 week. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2299 (884.4 mg, 40.1 %).

MS m/z: 504, ^{1}H-NMR d: 1.51 (3H, d, J=6.6Hz, CH_3), 2.33 (3H, d, J=6.3Hz, CH_3), 2.53 (1H, dt, J=6.1, 19.31Hz, CH_2), 2.66 (1H, t, J=6.1Hz, CH_2), 2.77-2.97 (2H, m, CH_2), 4.40 (2H, d, J=19.8Hz, CH_2), 4.59 (2H, d, J=24.9Hz, CH_2), 4.65-4.69 (1H, m, CH), 7.00 (1H, d, J=7.8Hz, Ar-H), 7.08 (1H, d, J=8.3Hz, Ar-H), 7.12 (1H, d, J=7.8Hz, Ar-H), 7.14 (1H, d, J=7.8Hz, Ar-H), 7.20 (1H, d, J=8.1Hz, Ar-H), 7.30 (1H, d, J=8.1Hz, Ar-H), 7.43-7.51 (3H, m, Ar-H), 7.53 (1H, d, J=8.3Hz, Ar-H), 7.57 (1H, d, J=8.1Hz, Ar-H), 7.68 (1H, d, J=6.8Hz, Ar-H), 7.73 (1H, dd, J=3.2, 8.1Hz, Ar-H), 7.86 (1H, dd, J=2.2, 7.6Hz, Ar-H), 8.17 (1H, d, J=7.6Hz, Ar-H).

Example 117: Synthesis of K-2300 (N1,N1-di(4-methylbenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0407] 4-Tolualdehyde (500 mg, 3.56 mmol) and 4-methylbenzylamine (503.6 mg, 3.56 mmol, 1.0 mol eq.) were dissolved in methanol and $MgSO_4$ (514.2 mg, 4.27 mmol, 1.2 mol eq.) and AcOH (3 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 50 minutes. After the completion of the reaction, sodium boron hydride (168.3 mg, 4.45 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 15 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column

chromatography [silica gel, hexane : ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 247 (819.4 mg, 88.2 %).

MS m/z: 225, ^{1}H-NMR d: 2.33 (6H, s, CH_3×2), 3.75 (4H, s, CH_2×2), 7.13 (4H, d, J=7.8Hz, Ar-H), 7.22 (4H, d, J=7.8Hz, Ar-H).

[0408] The dibenzylamine compound 247 (500 mg, 2.22 mmol) and triethylamine (0.372 ml, 2.67 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (221 mg, 2.44 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 248 (534.5 mg, 86.3 %).

MS m/z: 279, ^{1}H-NMR d: 2.34 (3H, s, CH_3), 2.35 (3H, s, CH_3), 4.45 (2H, s, CH_2), 4.60 (2H, s, CH_2), 5.71 (1H, dd, J=2.2, 10.2Hz, CH=CH_2), 6.47 (1H, dd, J=2.2, 16.6Hz, CH=CH_2), 6.60 (1H, dd, J=10.2, 16.6Hz, CH=CH_2), 7.05 (2H, d, J=7.8Hz, Ar-H), 7.13-7.17 (6H, m, Ar-H).

[0409] The conjugated ketone compound 248 (400 mg, 1.43 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (295 mg, 1.72 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 2 weeks. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2300 (372.5 mg, 57.9 %). Subsequently, the obtained K-2300 (253.6 mg, 0.56 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 15 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallized from ethanol/water to thereby give K-2300 hydrochloride (113.7 mg, 41.4 %) as colorless crystals.

MS m/z: 450, ^{1}H-NMR d: 1.57 (3H, d, J=6.6Hz, CH_3), 2.34 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.60-2.71 (2H, m, CH_2), 2.85-2.97 (2H, m, CH_2), 4.35 (2H, s, CH_2), 4.52 (1H, d, J=14.6Hz, CH_2), 4.59 (1H, d, J=14.6Hz, CH_2), 4.74 (1H, q, J=6.6Hz, CH), 7.00 (2H, d, J=8.1Hz, Ar-H), 7.11 (4H, d, J=1.2Hz, Ar-H), 7.14 (2H, d, J=7.8Hz, Ar-H), 7.45-7.52 (3H, m, Ar-H), 7.74 (1H, d, J=7.8Hz, Ar-H), 7.75 (1H, d, J=8.8Hz, Ar-H), 7.87 (1H, dd, J=2.2, 7.8Hz, Ar-H), 8.14 (1H, d, J=7.8Hz, Ar-H).

Example 118: Synthesis of K-2309 (N1-(3,4-dichlorobenzyl)-N1-(4-methoxybenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl)amino}propanamide)

[0410] 3,4-Dichlorobenzaldehyde (702 mg, 4.01 mmol, 1.1 mol eq.) and 4-methoxybenzylamine (0.476 ml, 3.64 mmol) were dissolved in methanol and $MgSO_4$ (525.8 mg, 4.37 mmol, 1.2 mol eq.) and AcOH (5 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, sodium boron hydride (172 mg, 4.55 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 20 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane : ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 249 (827.0 mg, 76.8 %).

MS m/z: 296, ^{1}H-NMR d: 3.72 (2H, s, CH_2), 3.74 (2H, s, CH_2), 3.80 (3H, s, OCH_3), 6.87 (2H, d, J=8.8Hz, Ar-H), 7.18 (1H, dd, J=2.0, 8.3Hz, Ar-H), 7.24 (2H, d, J=8.3Hz, Ar-H), 7.38 (1H, d, J=8.1Hz, Ar-H), 7.45 (1H, d, J=2.0Hz, Ar-H).

[0411] The dibenzylamine compound 249 (711.2 mg, 2.41 mmol) and triethylamine (0.402 ml, 2.89 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (240 mg, 2.65 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 45 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 250 (837.2 mg, 99.3 %).

MS m/z: 350, ^{1}H-NMR d: 3.81 (3H, s, OC$\underline{H}_3$), 4.50 (2H, d, J=44.2Hz, C$\underline{H}_2$), 4.54 (2H, d, J=49.3Hz, C$\underline{H}_2$), 5.78 (1H, dd, J=1.7, 10.2Hz, CH=C$\underline{H}_2$), 6.59 (1H, dd, J=1.7, 16.6Hz, C$\underline{H}$=CH$_2$), 6.65 (1H, dd, J=10.2, 16.6Hz, CH=C$\underline{H}_2$), 6.89 (2H, d, J=8.5Hz, Ar-H), 7.07 (2H, d, J=8.5Hz, Ar-H), 7.09 (1H, d, J=8.3Hz, Ar-H), 7.30 (1H, s, Ar-H), 7.38 (1H, d, J=8.3Hz, Ar-H).

[0412] The conjugated ketone compound 250 (692.4 mg, 1.98 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (407 mg, 2.37 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 2 weeks. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2309 (835.9 mg, 81.0 %). Subsequently, the obtained K-2309 (630.1 mg, 1.21 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 15 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallized from ethanol/water to thereby give K-2309 hydrochloride (566.8 mg, 84.0 %) as colorless crystals.

MS m/z: 521, ^{1}H-NMR d: 1.55 (3H, d, J=6.3Hz, C$\underline{H}_3$), 2.55-2.70 (2H, m, C$\underline{H}_2$), 2.86-2.97 (2H, m, C$\underline{H}_2$), 3.80 (3H, d, J=3.4Hz, OC$\underline{H}_3$), 4.33 (2H, d, J=12.7Hz, C$\underline{H}_2$), 4.51 (2H, d, J=8.8Hz, C$\underline{H}_2$), 4.68-4.73 (1H, m, C$\underline{H}$), 6.85 (2H, d, J=8.8Hz, Ar-H), 7.02 (2H, d, J=8.5Hz, Ar-H), 7.11 (1H, d, J=8.5Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.35 (1H, d, J=8.3Hz, Ar-H), 7.45-7.52 (3H, m, Ar-H), 7.70 (1H, t, J=6.8Hz, Ar-H), 7.75 (1H, d, J=8.3Hz, Ar-H), 7.87 (1H, dd, J=2.2, 7.8Hz, Ar-H), 8.16 (1H, d, J=7.8Hz, Ar-H).

Example 119: Synthesis of K-2310 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

[0413] 4-(Trifluoromethoxy)benzaldehyde (0.648 ml, 4.54 mmol, 1.1 mol eq.) and 4-methylbenzylamine (0.525 ml, 4.13 mmol) were dissolved in methanol and $MgSO_4$ (596.6 mg, 4.96 mmol, 1.2 mol eq.) and AcOH (5 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 40 minutes. After the completion of the reaction, sodium boron hydride (195 mg, 5.16 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 20 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane : ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 251 (979.1 mg, 80.4 %).

MS m/z: 295, ^{1}H-NMR d: 2.34 (3H, s, C$\underline{H}_3$), 3.76 (2H, s, C$\underline{H}_2$), 3.79 (2H, s, C$\underline{H}_2$), 7.14 (2H, d, J=8.1Hz, Ar-H), 7.16 (2H, d, J=8.5Hz, Ar-H), 7.22 (2H, d, J=8.1Hz, Ar-H), 7.36 (2H, d, J=8.5Hz, Ar-H).

[0414] The dibenzylamine compound 251 (846.8 mg, 2.87 mmol) and triethylamine (0.480 ml, 3.44 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (286 mg, 3.16 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 45 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 252 (844.5 mg, 84.3 %).

MS m/z: 349, ^{1}H-NMR d: 2.34 (3H, d, J=6.8Hz, C$\underline{H}_3$), 4.55 (2H, d, J=49.0Hz, C$\underline{H}_2$), 4.56 (2H, d, J=50.2Hz, C$\underline{H}_2$), 5.75 (1H, dd, J=2.2, 10.0Hz, CH=C$\underline{H}_2$), 6.49 (1H, dd, J=2.2, 16.8Hz, C$\underline{H}$=CH$_2$), 6.62 (1H, dd, J=10.0, 16.8Hz, CH=C$\underline{H}_2$), 7.04 (2H, d, J=7.8Hz, Ar-H), 7.13-7.21 (4H, m, Ar-H), 7.28 (2H, d, J=8.5Hz, Ar-H).

[0415] The conjugated ketone compound 252 (685.1 mg, 1.96 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (403 mg, 2.36 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 12 days. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2310 (777.8 mg, 76.3 %). Subsequently, the obtained K-2310 (539.0 mg, 1.04 mmol) was dissolved in a 10 % solution of hydrochloric acid/methanol and stirred for 15 minutes. Then it was concentrated as such under reduced pressure. The crystals thus formed were recrystallized from ethanol/water to thereby give K-2310 hydrochloride (493.0 mg, 85.1 %) as colorless crystals.

MS m/z: 520, ^{1}H-NMR d: 1.52 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.34 (3H, d, J=5.4Hz, C$\underline{H}_3$), 2.62 (2H, dt, J=5.9, 21.7Hz, C$\underline{H}_2$), 2.84-2.96 (2H, m, C$\underline{H}_2$), 4.38 (2H, s, C$\underline{H}_2$), 4.56 (2H, d, J=8.6Hz, C$\underline{H}_2$), 4.67 (1H, q, J=6.6Hz, C$\underline{H}$), 7.00 (2H, d, J=8.1Hz, Ar-H), 7.07-7.18 (4H m, Ar-H), 7.22 (2H, d, J=8.6Hz, Ar-H), 7.44-7.51 (3H, m, Ar-H), 7.68 (1H, d, J=6.6Hz, Ar-H), 7.73 (1H, d, J=8.1Hz, Ar-H), 7.86 (1H, dd, J=2.2, 8.1Hz, Ar-H), 8.16 (1H, d, J=8.5Hz, Ar-H).

Example 120: Synthesis of K-2311

[0416] 4-(Trifluoromethoxy)benzaldehyde (0.573 ml, 4.01 mmol, 1.1 mol eq.) and 4-methoxybenzylamine (0.476 ml, 3.64 mmol) were dissolved in methanol and $MgSO_4$ (525.8 mg, 4.37 mmol, 1.2 mol eq.) and AcOH (5 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, sodium boron hydride (172 mg, 4.55 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane : ethyl acetate (9 : 1 - 4 : 1)] to thereby give a colorless oil 253 (944.0 mg, 83.4 %).

MS m/z: 311, ^{1}H-NMR d: 3.74 (2H, s, C$\underline{H}_2$), 3.79 (2H, s, C$\underline{H}_2$), 3.80 (3H, s, OC$\underline{H}_3$), 6.87 (2H, d, J=8.5Hz, Ar-H), 7.17 (2H, d, J=8.3Hz, Ar-H), 7.25 (2H, d, J=8.3Hz, Ar-H), 7.37 (2H, d, J=8.5Hz, Ar-H).

[0417] The dibenzylamine compound 253 (766.5 mg, 2.46 mmol) and triethylamine (0.411 ml, 2.95 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (245 mg, 2.71 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 45 minutes. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 254 (749.0 mg, 83.4 %).

MS m/z: 365, ^{1}H-NMR δ: 3.80 (3H, s, OC$\underline{H}_3$), 4.48 (2H, d, J=13.4Hz, C$\underline{H}_2$), 4.60 (2H, d, J=12.4Hz, C$\underline{H}_2$), 5.76 (1H, dd, J=2.0, 10.2Hz, CH=C$\underline{H}_2$), 6.49 (1H, dd, J=2.0, 16.8Hz C$\underline{H}$=C$\underline{H}_2$), 6.65 (1H, dd, J=10.2, 16.8Hz, CH=C$\underline{H}_2$), 6.84 (1H, d, J=8.5Hz, Ar-H), 6.88 (1H, d, J=8.5Hz, Ar-H), 7.07 (1H, d, J=8.3Hz, Ar-H), 7.16 (1H, d, J=8.8Hz, Ar-H), 7.18 (3H, d, J=7.6Hz, Ar-H), 7.27 (1H, d, J=9.5Hz, Ar-H).

[0418] The conjugated ketone compound 254 (612.8 mg, 1.68 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (345 mg, 2.01 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 12 days. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil K-2311 (668.3 mg, 74.2 %).

MS m/z: 536, ^{1}H-NMR d: 1.53 (3H, d, J=6.6Hz, C$\underline{H}_3$), 2.55-2.73 (2H, m, C$\underline{H}_2$), 2.84-2.96 (2H, m, C$\underline{H}_2$), 3.79 (3H, d, J=3.2Hz, OC$\underline{H}_3$), 4.36 (2H, d, J=10.0Hz, C$\underline{H}_2$), 4.54 (2H, d, J=12.9Hz, C$\underline{H}_2$), 4.70 (1H, q, J=6.6Hz, C$\underline{H}$), 6.82 (1H, d, J=8.8Hz, Ar-H), 6.85 (1H, d, J=8.8Hz, Ar-H), 7.02 (1H, d, J=8.5Hz, Ar-H), 7.12 (1H, d, J=8.8Hz, Ar-H), 7.13-7.18 (3H, m, Ar-H), 7.22 (1H, d, J=8.5Hz, Ar-H), 7.45-7.51 (3H, m, Ar-H), 7.70 (1H, t, J=6.6Hz, Ar-H), 7.74 (1H, d, J=8.3Hz, Ar-H), 7.86 (1H, d, J=8.1Hz, Ar-H), 8.16 (1H, d, J=8.1Hz, Ar-H).

Example 121: Synthesis of K-2312

[0419] 4-Hydroxybenzaldehyde (490 mg, 4.01 mmol, 1.1 mol eq.) and 4-methoxybenzylamine (0.476 ml, 3.64 mmol) were dissolved in methanol and $MgSO_4$ (525.8 mg, 4.37 mmol, 1.2 mol eq.) and AcOH (5 drops) were added thereto. Then the obtained mixture was stirred at room temperature for 45 minutes. After the completion of the reaction, sodium boron hydride (172 mg, 4.55 mmol, 1.25 mol eq.) was added to the reaction mixture. Then the obtained mixture was stirred at room temperature for 10 minutes. After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, chloroform/methanol] to thereby give a colorless oil 255 (858.9 mg, 97.1 %).

MS m/z: 243, ^{1}H-NMR δ: 3.69 (2H, s, CH_2), 3.77 (2H, s, CH_2), 3.79 (3H, s, OCH_3), 6.64 (2H, d, J=8.5Hz, Ar-H), 6.86 (2H, d, J=8.8Hz, Ar-H), 7.09 (2H, d, J=8.5Hz, Ar-H), 7.26 (2H, d, J=8.5Hz, Ar-H).

[0420] The dibenzylamine compound 255 (521.4 mg, 2.15 mmol) and triethylamine (0.359 ml, 2.57 mmol, 1.2 mol eq.) were dissolved in chloroform and acryloyl chloride (214 mg, 2.36 mmol, 1.1 mol eq.) dissolved in chloroform was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent, the oil thus obtained was purified by column chromatography [silica gel, chloroform] to thereby give a colorless oil 256 (375.5 mg, 58.8 %).

MS m/z: 297, ^{1}H-NMR δ: 3.80 (3H, d, J=6.8Hz, OCH_3), 4.44 (2H, d, J=16.1Hz, CH_2), 4.56 (2H, d, J=9.0Hz, CH_2), 5.76 (1H, dd, J=2.2, 10.2Hz, CH=CH_2), 6.48 (1H, ddd, J=2.2, 7.1, 16.6Hz, CH=CH_2), 6.64 (1H, ddd, J=3.2, 10.2, 16.6Hz, CH=CH_2), 6.79 (1H, d, J=8.5Hz, Ar-H), 6.83 (1H, d, J=8.5Hz, Ar-H), 6.85 (1H, d, J=8.5Hz, Ar-H), 6.89 (1H, d, J=8.5Hz, Ar-H), 6.98 (1H, d, J=8.3Hz, Ar-H), 7.08 (1H, d, J=6.8Hz, Ar-H), 710 (1H, d, J=6.8Hz, Ar-H), 7.19 (1H, d, J=8.5Hz, Ar-H).

[0421] The conjugated ketone compound 256 (260.2 mg, 0.88 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (180 mg, 1.05 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4 : 1) and allowed to stand at room temperature for 13 days. After the completion of the reaction, the solvent was distilled off under reduced pressure and the oil thus obtained was purified by column chromatography [silica gel, chloroform/methanol] to thereby give a colorless oil K-2312 (177.4 mg, 43.3 %).

MS m/z: 468, ^{1}H-NMR δ: 1.61 (3H, d, J=6.8Hz, CH_3), 2.63-2.71 (1H, m, CH_2), 2.81-2.88 (2H, m, CH_2), 2.95 (1H, d, J=5.4Hz, CH_2), 3.78 (3H, d, J=5.4Hz, OCH_3), 4.22 (2H, d, J=18.3Hz, CH_2), 4.27 (2H, d, J=30.5Hz, CH_2), 4.81-4.86 (1H, m, CH), 6.72 (1H, d, J=8.5Hz, Ar-H), 6.74 (1H, d, J=8.5Hz, Ar-H), 6.82 (1H, d, J=8.8Hz, Ar-H), 6.83 (1H, d, J=8.5Hz, Ar-H), 6.85 (1H, d, J=8.5Hz, Ar-H), 6.98 (1H, d, J=8.8Hz, Ar-H), 7.02 (1H, d, J=8.5Hz, Ar-H), 7.10 (1H, d, J=8.5Hz, Ar-H), 7.45-7.54 (3H, m, Ar-H), 7.77 (2H, d, J=7.6Hz, Ar-H), 7.88 (1H, d, J=8.1Hz, Ar-H), 8.11 (1H, d, J=8.1Hz, Ar-H).

Example 122: Synthesis of K-2280 (N-[5-[(4-methoxyphenyl)thio]pentyl-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0422] 4-Methoxythiophenol (753 mg, 5.37 mmol) was dissolved in acetonitrile (10 ml). To the obtained solution were successively added at room temperature potassium carbonate (754 mg, 5.46 mmol) and 1,5-dibromopentane (0.73 ml, 5.35 mmol) and the reaction mixture was stirred at room temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (931 mg, 6.75 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.52 ml, 3.22 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred at 85 °C for 12 hours. After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was added thereto. Next, the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give a pale yellow, syrupy compound K-2280 as a free compound. Subsequently, 5 ml of 10 % hydrochloric acid/methanol was poured into the K-2280 obtained above and allowed to stand for 3 minutes followed by concentration. The pale yellow crystals thus obtained were subjected to Kiriyama's filtration and the precipitate was washed with diethyl ether. Thus 210 mg (0.55 mmol, yield: 20.6 %) of K-2280 hydrochloride was obtained as white crystals.

400MHz-NMR 10.49 (1H, bs), 9.98 (1H, bs), 8.24 (1H, d, J=7.32Hz), 7.98 (1H, d, J=8.56Hz), 7.94 (1H, dd, J=8.04Hz, J=1.48Hz), 7.90 (1H, d, J=8.28Hz), 7.52-7.68 (3H, m), 7.19-7.23 (2H, m), 6.73-6.77 (2H, m), 5.14-5.24 (1H, m), 3.73 (3H, s), 2.67-2.75 (2H, m), 2.65 (2H, t, J=7.20Hz), 2.02 (3H, d, J=6.84Hz), 1.91-1.99 (2H, m), 1.38-1.46 (2H, m), 1.21-1.35 (2H, m), m/z=379.

Example 123: Synthesis of K-2281 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[4-[(2,4,5-trichlorophenyl)thio]butyl]amine)

[0423] 2,4,5-Trichlorothiophenol (770 mg, 3.61 mmol) was dissolved in acetonitrile (10 ml). To the obtained solution were successively added at room temperature potassium carbonate (560 mg, 4.05 mmol) and 1,4-dibromobutane (0.43 ml, 3.60 mmol) and the reaction mixture was stirred at room temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (545 mg, 3.94 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.41 ml, 3.94

mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred at 85 °C for 12 hours. After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was added thereto. Next, the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200:1) to thereby give a pale yellow, syrupy compound K-2281 as a free compound. Subsequently, 10 ml of 10 % hydrochloric acid/methanol was poured into the K-2281 obtained above and allowed to stand for 5 minutes followed by concentration. The pale yellow crystals thus obtained were subjected to Kiriyama's filtration and the precipitate was washed with diethyl ether. Thus 280 mg (0.59 mmol, yield: 15.0 %) of K-2281 hydrochloride was obtained as white crystals.

400MHz-NMR 10.64 (1H, bs), 10.07 (1H, bs), 8.26 (1H, dd, J=7.3Hz, J=0.7Hz), 8.01 (1H, d=8.3Hz), 7.90-7.95 (2H, m), 7.52-7.68 (3H, m), 7.36 (1H, s), 7.11 (1H, s), 5.20-5.26 (1H, m), 2.76 (2H, t, J=7.0Hz), 2.76-2.82 (2H, m), 2.87 (3H, d, J=6.8Hz), 1.53-1.63 (2H, m), m/z=437, 439.

Example 124: Synthesis of K-2282 (N-[(1R)-1-(1-naphthyl)ethyl]-N-{5-[(2,4,5-trichlorophenyl)thio]pentyl}amine)

[0424] 2,4,5-Trichlorothiophenol (1.53 g, 7.15 mmol) was dissolved in acetonitrile (15 ml). To the obtained solution were successively added at room temperature potassium carbonate (1.083 g, 7.84 mmol) and 1,5-dibromopentane (0.98 ml, 7.19 mmol) and the reaction mixture was stirred at room temperature for 2.5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.00 g, 7.25 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.69 ml, 4.27 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred at 85 °C for 12 hours. After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was added thereto. Next, the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give a pale yellow, syrupy compound K-2282 as a free compound. Subsequently, 15 ml of 10 % hydrochloric acid/methanol was poured into the K-2282 obtained above and allowed to stand for 5 minutes followed by concentration. The pale yellow crystals thus obtained were subjected to Kiriyama's filtration and the precipitate was washed with diethyl ether. Thus 283 mg (0.58 mmol, yield: 13.5 %) of K-2282 hydrochloride was obtained as white crystals.

400MHz-NMR 10.55 (1H, bs), 10.03 (1H, bs), 8.25 (1H, d, J=7.3Hz), 8.00 (1H, d, J=8.5Hz), 7.90-7.95 (2H, m), 7.54-7.68 (3H, m), 7.37 (1H, s), 7.16 (1H, s), 5.17-5.26 (1H, m), 2.73-2.82 (4H, m), 1.97-2.05 (2H, m), 2.05 (3H, d, J=6.6Hz), 1.52-1.60 (2H, m), 1.31-1.45 (2H, m), m/z=451, 453.

Example 125: Synthesis of K-2287 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-{[4-(trifluoromethoxy)phenyl)thio]butyl)amine)

[0425] 4-Trifluoromethoxythiophenol (908 mg, 4.68 mmol) was dissolved in acetonitrile (10 ml). To the obtained solution were successively added at room temperature potassium carbonate (679 mg, 4.91 mmol) and 1,4-dibromobutane (0.568 ml, 4.69 mmol) and the reaction mixture was stirred at room temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (710 mg, 5.14 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.53 ml, 3.28 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred at 90 °C for 12 hours. After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was added thereto. Next, the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give a pale yellow, syrupy compound K-2287 as a free compound. Subsequently, 10 ml of 10 % hydrochloric acid/methanol was poured into the K-2287 obtained above and allowed to stand for 5 minutes followed by concentration. The pale yellow crystals thus obtained were subjected to Kiriyama's filtration and the precipitate was washed with hexane. Thus 245 mg (0.54 mmol, yield: 16.5 %) of K-2287 hydrochloride was obtained as white crystals.

400MHz-NMR 10.58 (1H, bs), 10.07 (1H, bs), 8.25 (1H, d, J=6.8Hz), 8.00 (1H, d, J=8.5Hz), 7.90-7.96 (2H, m), 7.52-7.67 (3H, m), 7.15-7.19 (3H, m), 7.02-7.04 (2H, m), 5.19-5.24 (1H, m), 2.73-2.76 (4H, m), 2.06-2.17 (2H, m), 2.06 (3H, d, J=6.8Hz), 1.41-1.59 (2H, m), m/z=419.

Example 126: Synthesis of K-2288 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[[4-(trifluoromethoxy)phenyl)thio)pentyl)amine)

[0426] 4-Trifluoromethoxythiophenol (995 mg, 5.12 mmol) was dissolved in acetonitrile (10 ml). To the obtained solution were successively added at room temperature potassium carbonate (715 mg, 5.17 mmol) and 1,5-dibromopentane (0.70 ml, 5.14 mmol) and the reaction mixture was stirred at room temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (770 mg, 5.57 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.58 ml, 3.59 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred at 85 °C for 12 hours. After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was added thereto. Next, the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give a pale yellow, syrupy compound K-2288 as a free compound. Subsequently, 10 ml of 10 % hydrochloric acid/methanol was poured into the K-2288 obtained above and allowed to stand for 5 minutes followed by concentration. The pale yellow crystals thus obtained were subjected to Kiriyama's filtration and the precipitate was washed with hexane. Thus 313 mg (0.67 mmol, yield: 18.7 %) of K-2288 hydrochloride was obtained as white crystals.

400MHz-NMR 10.53 (1H, m), 10.03 (1H, bs), 8.24-8.26 (1H, m), 7.99 (1H, d, J=8.3Hz), 7.52-7.67 (3H, m), 7.19-7.23 (2H, m), 7.04-7.07 (2H, m), 5.15-5.25 (1H, m), 2.76 (2H, t, J=7.2Hz), 2.69-2.78 (2H, m), 2.03 (3H, d, J=6.8Hz), 1.92-2.04 (2H, m), 1.49 (2H, tt, J=7.4Hz, J=7.4Hz), 1.27-1.38 (2H, m), m/z=433. Example 127: Synthesis of K-2293 (N-[4-[(4-chlorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0427] 4-Chlorothiophenol (782 mg, 5.41 mmol) was dissolved in acetonitrile (10 ml). To the obtained solution were successively added at room temperature potassium carbonate (850 mg, 6.15 mmol) and 1,4-dibromobutane (0.65 ml, 5.44 mmol) and the reaction mixture was stirred at room temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (775 mg, 5.61 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.62 ml, 3.84 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred at 85 °C for 24 hours. After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was added thereto. Next, the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give a pale yellow, syrupy compound K-2293 as a free compound. Subsequently, 10 ml of 10 % hydrochloric acid/methanol was poured into the K-2293 obtained above and allowed to stand for 5 minutes followed by concentration. The pale yellow crystals thus obtained were subjected to Kiriyama's filtration and the precipitate was washed with diethyl ether. Thus 420 mg (1.03 mmol, yield: 26.9 %) of K-2293 hydrochloride was obtained as white crystals.

400MHz-NMR 10.58 (1H, bs), 10.05 (1H, bs), 8.25 (1H, d, J=6.8Hz), 7.99 (1H, d, J=8.3Hz), 7.94 (1H, dd, J=8.0Hz, J=1.2Hz), 7.91 (1H, d, J=8.04Hz), 7.52-7.67 (3H, m), 7.12-7.16 (2H, m), 7.06-7.10 (2H, m), 5.16-5.25 (1H, m), 2.70-2.74 (4H, m), 2.06-2.15 (2H, m), 2.05 (3H, d, J=6.6Hz), 1.40-1.57 (2H, m), m/z=369.

Example 128: Synthesis of K-2240 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(3-[[4-(trifluoromethyl)phenyl]thio]propyl)amine)

[0428] K-2240 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 4-trifluoromethylthiophenol and 1,3-dibromopropane. m/z = 389.

Example 129: Synthesis of K-2263 (N-[4-[(4-fluorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0429] K-2263 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 4-fluorothiophenol.

400MHz-NMR 10.57 (1H, bs), 10.04 (1H, bs), 8.24 (1H, d, J=7.3Hz), 7.99 (1H, d, J=8.52Hz), 7.90-7.96 (2H, m), 7.52-7.67 (3H, m), 7.15-7.20 (2H, m), 6.86-6.92 (2H, m), 5.19-5.22 (1H, m), 2.67-2.77 (2H, m), 2.69 (2H, t, J=7.1Hz), 2.05-2.15 (2H, m), 2.05 (3H, d, J=6.8Hz), 1.36-1.54 (2H, m), m/z=353.

Example 130: Synthesis of K-2269 (N-{4-[(3-methoxyphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0430] K-2269 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 3-methoxythiophenol.

400MHz-NMR 10.58 (1H, bs), 10.06 (1H, bs), 8.24-8.26 (1H, m), 7.99 (1H, d, J=8.3Hz), 7.88-7.94 (3H, m), 7.53-7.67 (3H, m), 7.08 (1H, dd, J=8.3Hz, J=8.3Hz), 6.71-6.74 (2H, m), 6.64 (1H, ddd, J=8.3Hz, J=2.4Hz, J=1.0Hz), 5.15-5.25 (1H, m), 2.70-2.79 (2H, m), 2.75 (2H, t, J=7.2Hz), 2.07-2.16 (2H, m), 2.05 (3H, d, J=6.8Hz), 1.43-1.60 (2H, m), m/z=365.

Example 131: Synthesis of K-2271 (N-{[4-(5-ethoxy-1,3-benzothiazol-2-yl)thio]butyl-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0431] K-2271 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 6-ethoxy-2-mercaptobenzothiazole.

400MHz-NMR 10.56 (1H, bs), 10.04 (1H, bs), 8.29 (1H, d, J=7.0Hz), 8.02 (1H, d, J=8.5Hz), 7.87-7.92 (2H, m), 7.52-7.70 (4H, m), 7.13 (1H, d, J=2.2Hz), 6.96 (1H, dd, J=8.8Hz, J=2.2Hz), 5.20-5.28 (1H, m), 4.02 (2H, dd, J=13.9Hz, J=7.1Hz), 3.27 (2H, dd, J=7.1Hz, J=7.1Hz), 2.20-2.60 (4H, m), 2.12-2.23 (2H, m), 2.06 (3H, d, J=6.6Hz), 1.76-1.87 (2H, m), 1.42 (3H, t, J=6.8Hz), m/z=436.

Example 132: Synthesis of K-2279 (N-{[5-(3-methoxyphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0432] K-2279 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 3-methoxythiophenol and 1,5-dibromopentane.

400MHz-NMR 10.51 (1H, bs), 9.99 (1H, bs), 8.24 (1H, d, J=7.1Hz), 7.89-7.99 (3H, m), 7.54-7.67 (3H, m), 7.10 (1H, dd, J=7.9Hz, J=7.9Hz), 6.75-6.79 (2H, m), 6.61-6.65 (1H, ddd, J=8.0Hz, J=2.4Hz, J=0.7Hz), 5.14-5.24 (1H, m), 3.72 (3H, s), 2.68-2.79 (4H, m), 2.03 (3H, d, J=6.8Hz), 1.93-1.99 (2H, m), 1.47-1.54 (2H, m), 1.24-1.38 (2H, m), m/z=379.

Example 133: Synthesis of K-2284 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-{[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio}pentyl)amine)

[0433] K-2284 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol and 1,5-dibromopentane.

400MHz-NMR 10.54 (1H, bs), 10.43 (1H, bs), 8.24 (1H, d, J=6.6Hz), 7.99 (1H, d, J=8.3Hz), 7.90-7.96 (2H, m), 7.55-7.67 (3H, m), 5.15-5.25 (1H, bs), 2.91 (2H, t, J=7.2Hz), 2.70-2.80 (2H, m), 2.04 (3H, d, J=6.6Hz), 1.93-2.02 (2H, m), 1.48 (2H, tt, J=7.4Hz, J=7.4Hz), 1.26-1.41 (2H, m), m/z=489.

Example 134: Synthesis of K-2286 (N-{6-[(4-chlorophenyl)thio]hexyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0434] K-2286 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 1,4-dibromobutane by 1,6-dibromohexane. m/z = 397.

Example 135: Synthesis of K-2292 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(7-{[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio}heptyl)amine)

[0435] K-2292 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 2,3,5,6-tetrafluoro-4-trifluorometylthiophenol and 1,7-dibromopentane.

400MHz-NMR 10.48 (1H, bs), 9.98 (1H, bs), 8.26 (1H, d, J=6.8Hz), 8.00 (1H, d, J=8.3Hz), 7.94 (1H, d, J=7.3Hz), 7.91 (1H, d, J=8.0Hz), 7.54-7.68 (3H, m), 5.21 (1H, bs), 2.92 (2H, t, J=7.3Hz), 2.74 (2H, bs), 2.05 (3H, d, J=5.1Hz), 1.97 (2H, bs), 1.42-1.50 (2H, m), 1.23-1.38 (2H, m), 1.17 (4H, bs), m/z=517.

Example 136: Synthesis of K-2295

[0436] K-2295 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 2,4,5-trichlorothiophenol and 1-bromo-2-chloroethane.

400MHz-NMR 10.94 (1H, bs), 10.31 (1H, bs), 8.17 (1H, d, J=6.6Hz), 7.88-7.96 (3H, m), 7.55-7.65 (3H, m), 7.42 (1H, s), 7.29 (1H, s), 5.20-5.28 (1H, m), 3.47-3.59 (2H, m), 2.92-3.07 (2H, m), 2.03 (3H, d, J=6.6Hz), m/z=409.

Example 137: Synthesis of K-2296 (N-{[5-(2,5-dichlorophenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0437] K-2296 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 2,5-dichlorothiophenol and 1,5-dibromopentane.

400MHz-NMR 10.63 (1H, bs), 10.08 (1H, bs), 8.26 (1H, d, J=6.8Hz), 8.01 (1H, d, =8.5Hz), 7.90-7.94 (2H, m), 7.52-7.68 (3H, m), 7.18 (1H, d, J=8.3Hz), 6.98-7.02 (2H, m), 5.18-5.28 (1H, m), 2.75-2.84 (2H, m), 2.77 (2H, t, J=7.2Hz), 2.12-2.20 (2H, m), 2.07 (3H, d, J=6.6Hz), 1.56-1.67 (4H, m), m/z=417.

Example 138: Synthesis of K-2297 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-{[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio}butyl)amine)

[0438] K-2297 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol.

400MHz-NMR 10.59 (1H, bs), 10.08 (1H, b), 8.23 (1H, d, J=6.6Hz), 8.00 (1H, d, J=8.3Hz), 7.94 (1H, dd, J=8.0Hz, J=1.2Hz), 7.55-7.67 (3H, m), 5.18-5.23 (1H, m), 2.89 (2H, t, J=7.3Hz), 2.70-2.82 (2H, m), 2.04-2.13 (2H, m), 2.05 (3H, d, J=6.6Hz), 1.47-1.60 (2H, m), m/z=475.

Example 139: Synthesis of K-2298 (N-{4-[(2,5-dichlorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

[0439] K-2298 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 2,5-dichlorothiophenol.

400MHz-NMR 10.64 (1H, bs), 10.09 (1H, bs), 8.26 (1H, d, J=6.6Hz), 8.01 (1H, d, J=8.3Hz), 7.89-7.94 (2H, m), 7.52-7.68 (3H, m), 7.18 (1H, d, J=8.3Hz), 7.01 (1H, dd, J=6.6Hz, J=2.4Hz), 5.18-5.28 (1H, m), 2.73-2.85 (2H, m), 2.76 (2H, t, J=7.2Hz), 2.16 (2H, tt, J=7.2Hz, J=7.2Hz), 2.07 (3H, d, J=6.8Hz), 1.52-1.68 (2H, m), m/z=403.

Example 140: Synthesis of K-2301 (N-[(1R)-1-((1-naphthyl)ethyl]-N-(6-{[4-(trifluoromethoxy)phenyl]thio}hexyl)amine)

[0440] K-2301 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 4-trifluoromethoxythiophenol and 1,6-dibromohexane.

400MHz-NMR 10.53 (1H, bs), 10.00 (1H, bs), 8.27 (1H, d, J=7.3Hz), 8.00 (1H, d, J=8.3Hz), 7.89-7.95 (2H, m), 7.52-7.68 (3H, m), 7.21-7.24 (2H, m), 7.05-7.08 (2H, m), 5.21 (1H, bs), 2.70-2.78 (2H, m), 2.76 (2H, t, J=7.3Hz), 2.06 (3H, d, J=6.6Hz), 1.92-2.02 (2H, m), 1.46-1.54 (2H, m), 1.17-1.35 (4H, m), m/z=447.

Example 141: Synthesis of K-2302 (N-{4-[(2,4-dimethylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl)amine)

[0441] K-2302 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 2,4-dimethylthiophenol.

400MHz-NMR 10.60 (1H, bs), 10.05 (1H, bs), 8.25 (1H, d, J=7.3Hz), 7.99 (1H, d, J=8.6Hz), 7.93 (1H, d, J=7.84Hz), 7.89 (1H, d, J=8.3Hz), 7.51-7.66 (3H, m), 7.00 (1H, d, J=7.8Hz), 6.90 (1H, s), 6.83 (1H, d, J=7.8Hz), 5.15-5.24 (1H, m), 2.70-2.78 (2H, m), 2.66 (2H, t, J=7.2Hz), 2.22 (6H, s), 2.07-2.13 (2H, m), 2.05 (3H, d, J=6.8Hz), 1.40-1.55 (2H, m), m/z=363.

Example 142: Synthesis of K-2303 (N-{5-[(2,4-dimethylphenyl)thio)pentyl}-N-[(1R)-1-((1-naphthyl)ethyl]amine)

[0442] K-2303 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 2,4-dimethylthiophenol and 1,5-dibromohexane.

400MHz-NMR 10.51 (1H, bs), 10.00 (1H, bs), 8.25 (1H, d, J=7.1Hz), 7.98 (1H, d, J=8.3Hz), 7.94 (1H, dd, J=7.8Hz, J=1.2Hz), 7.90 (1H, d, J=8.3Hz), 7.53-7.67 (3H, m), 7.05 (1H, d, J=7.8Hz), 6.90 (1H, s), 6.85 (1H, d, J=7.8Hz), 5.14-5.23 (1H, m), 2.67-2.78 (2H, m), 2.67 (2H, t, J=7.3Hz), 2.24 (3H, s), 2.21 (3H, s), 2.02 (3H, d, J=6.6Hz), 1.92-2.01 (2H, m), 1.43-1.51 (2H, m), 1.27-1.34 (2H, m), m/z=377.

Example 143: Synthesis of K-2304 (N-[4-[(4-methylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl)amine)

[0443] K-2304 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 4-methylthiophenol.

400MHz-NMR 10.55 (1H, bs), 10.03 (1H, bs), 8.25 (1H, d, J=7.1Hz), 7.99 (1H, d, J=8.5Hz), 7.93-7.95 (1H, m), 7.89 (1H, d, J=8.0Hz), 7.06-7.86 (5H, m), 6.96-6.99 (2H, m), 5.18-5.22 (1H, m), 2.68-2.77 (2H, m), 2.69 (2H, t, J=7.2Hz), 2.25 (3H, s), 2.04-2.14 (2H, m), 2.04 (3H, d, J=6.6Hz), 1.37-1.55 (2H, m), m/z=349.

Example 144: Synthesis of K-2305 (N-{5-[(4-methylphenyl)thio]pentyl}-N-[(1R)-1-((1-naphthyl)ethyl]amine)

[0444] K-2305 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 4-methylthiophenol and 1,5-dibromopentane.

400MHz-NMR 10.50 (1H, bs), 9.99 (1H, bs), 8.25 (1H, d, J=7.1Hz), 7.98 (1H, d, J=8.3Hz), 7.94 (1H, dd, J=7.8Hz, J=1.2Hz), 7.89 (1H, d, J=8.3Hz), 7.52-7.66 (3H, m), 7.11-7.13 (2H, m), 6.98-7.00 (2H, m), 5.18 (1H, bs), 2.68-2.73 (2H, m), 2.71 (2H, t, J=7.2Hz), 2.24 (3H, s), 2.02 (3H, d, J=6.6Hz), 1.91-1.99 (2H, m), 1.42-1.50 (2H, m), 1.26-1.34 (2H, m), m/z=363.

Example 145: Synthesis of K-2275

[0445] K-2305 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol and 1,4-dibromobutane respectively by 3-trifluoromethylthiophenol and 1-bromo-2-chloroethane.

400MHz-NMR 10.88 (1H, bs), 10.25 (1H, bs), 8.16 (1H, d, J=6.6Hz), 7.87-7.95 (3H, m), 7.52-7.65 (3H, m), 7.40 (1H, bs), 7.31-7.34 (2H, m), 7.21-7.26 (1H, m), 5.18-5.28 (1H, m), 3.53 (2H, t, J=7.7Hz), 2.91-3.06 (2H, m), 2.01 (3H, d, J=6.84Hz), m/z=375.

Example 146: Synthesis of K-2314

[0446] K-2314 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol by 4-methoxythiophenol.

400MHz-NMR 10.55 (1H, bs), 10.03 (1H, bs), 8.25 (1H, d, J=7.4Hz), 7.99 (1H, d, J=8.5Hz), 7.89-7.95 (2H, m), 7.52-7.68 (3H, m), 7.15-7.18 (2H, m), 6.71-6.75 (2H, m), 5.18-5.22 (1H, m), 3.74 (3H, s), 2.67-2.76 (2H, m), 2.64 (2H, t, J=7.1Hz), 2.03-2.15 (2H, m), 2.05 (2H, d, J=6.8Hz), 1.32-1.50 (2H, m), m/z=365.

Example 147: Synthesis of K-2008

[0447] K-2008 hydrochloride was obtained as white crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine respectively by 3-trifluoromethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-methylbenzylamine. m/z = 355.

Example 148: Synthesis of S-1

[0448] 2,5-Dimethylthiophenol (580 mg, 4.20 mmol) was dissolved in acetonitrile (6 ml). To the obtained solution were successively added at room temperature potassium carbonate (785 mg, 5.68 mmol) and 1-bromo-2-chloroethane (0.35 ml, 4.21 mmol) and the reaction mixture was stirred at room temperature for 2.5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (730 mg, 5.28 mmol) and (R)-(+)-3-methoxy-α-benzylmethylamine (500 mg, 3.30 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred at 90 °C for 24 hours. After the completion of the reaction, the mixture was cooled by allowing to stand at room temperature and water was added thereto. Next, the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (chloroform : methanol = 200 : 1) to thereby give a pale yellow, syrupy compound S-1 (332 mg, 1.05 mmol, yield: 31.8 %).

500MHz-^{1}H-NMR 7.30 (1H, d, J=8.0Hz), 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 7.06 (1H, s), 6.86-6.90 (3H, m), 6.75-6.78 (1H, m), 3.80 (3H s), 3.74 (1H, q, J=6.5Hz), 2.95-3.03 (2H, m), 2.68-2.77 (2H, m), 2.32 (3H, s), 2.27 (3H, s), 1.34 (3H, d, J=6.5Hz), m/z=315.

Example 149: Synthesis of S-2

[0449] S-2 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane by 1,3-dibromopropane.

500MHz-^{1}H-NMR 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 7.06 (1H, s), 7.02 (1H, d, J=7.5Hz), 6.86-6.88 (3H, m), 6.76-6.78 (1H, m), 3.80 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.85-2.96 (2H, m), 2.53-2.66 (2H, m), 2.29 (3H, s), 2.28 (3H, s), 1.74-1.82 (2H, m), 1.33 (3H, d, J=6.5Hz), m/z=329.

Example 150: Synthesis of S-3

[0450] S-3 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane by 1,4-dibromobutane.

500MHz-^{1}H-NMR 7.22 (1H, dd, J=8.3Hz, J=8.3Hz), 7.04 (1H, s), 7.03 (1H, d, J=8.0Hz), 6.85-6.89 (3H, m), 6.75-6.78 (1H, m), 3.80 (3H, s), 3.71 (1H, q, J=6.8Hz), 2.85 (2H, t, J=7.3Hz), 2.42-2.55 (2H, m), 2.30 (3H, s), 2.29 (3H, s), 1.56-1.70 (4H, m), 1.33 (3H, d, J=6.8Hz), m/z=343.

Example 151: Synthesis of S-4

[0451] S-4 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane by 1,5-dibromopentane.

500MHz-^{1}H-NMR 7.23 (1H, dd, J=8.3Hz, J=8.3Hz), 7.05 (1H, s), 7.03 (1H, d, J=7.5Hz), 6.87-6.88 (3H, m), 6.76-6.78 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.85 (1H, t, J=7.5Hz), 2.40-2.51 (2H, m), 2.31 (3H, s), 2.30 (3H, s), 1.61-1.67 (2H, m), 1.42-1.51 (4H, m), 1.34 (3H, d, J=6.5Hz), m/z=357.

Example 152: Synthesis of S-5

[0452] S-5 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane by 1,6-dibromohexane.

500MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.05 (1H, s), 7.03 (1H, d, J=8.0Hz), 6.86-6.89 (3H, m), 6.76-6.78 (3H, m), 3.81 (3H, s), 3.72 (1H, q, J=7.0Hz), 2.85 (2H, t, J=7.3Hz), 2.39-2.52 (2H, m), 2.31 (3H, s), 2.30 (3H, s), 1.61-1.67 (2H, m), 1.39-1.50 (4H), 1.34 (3H, d, J=7.0Hz), 1.29-1.34 (2H, m), m/z=371.

Example 153: Synthesis of S-6

[0453] S-6 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane by 1,7-dibromoheptane.

500MHz-^{1}H-NMR 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 7.05 (1H, s), 7.03 (1H, d, J=7.5Hz), 6.80-6.86 (3H, m), 6.75-6.78 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.8Hz), 2.85 (2H, t, J=7.5Hz), 2.38-2.51 (2H, m), 2.31 (3H, s), 2.29 (3H, s), 1.60-1.66 (2H, m), 1.37-1.48 (4H, m), 1.34 (3H, d, J=6.8Hz), 1.27-1.30 (4H, m), m/z=385.

Example 154: Synthesis of S-7

[0454] S-7 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane by 1,8-dibromooctane.

500MHz-^{1}H-NMR 7.23 (1H, dd, J=8.3Hz, J=8.3Hz), 7.06 (1H, s), 7.03 (1H, d, J=8.0Hz), 6.87-6.89 (3H, m), 6.75-6.78 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.86 (2H, t, J=7.5Hz), 2.39-2.51 (2H, m), 2.31 (3H, s), 2.30 (3H, s), 1.61-1.67 (2H, m), 1.38-1.47 (4H, m), 1.34 (3H, d, J=6.5Hz), 1.23-1.31 (6H, m), m/z=399.

Example 155: Synthesis of S-8

[0455] S-8 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the (R)-(+)-3-methoxy-α-benzylmethylamine by (R)-(+)-1-(1-naphthyl)ethylamine.

500MHz-^{1}H-NMR 8.16 (1H, d, J=8.8Hz), 7.83-7.87 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.64 (1H, d, J=7.1Hz), 7.42-7.51 (3H, m), 7.05 (1H, s), 7.03 (1H, d, J=8.0Hz), 6.88 (1H, d, J=7.8Hz), 4.63 (1H, q, J=6.6Hz), 3.05 (2H, t, J=6.6Hz), 2.77-2.87 (2H, m), 2.32 (3H, s), 2.24 (3H, s), 1.49 (3H, d, J=6.6Hz), m/z=335.

Example 156: Synthesis of S-9

[0456] S-9 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

500MHz-^{1}H-NMR 8.18 (1H, d, J=8.3Hz), 7.83-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.64 (1H, d, J=6.8Hz), 7.44-7.52 (3H, m), 7.25 (1H, s), 7.06 (1H, s), 7.02 (1H, d, J=7.7Hz), 6.87 (1H, d, J=7.7Hz), 4.62 (1H, q, J=6.6Hz), 2.87-3.00 (2H, m), 2.64-2.77 (2H, m), 2.28 (3H, s), 2.27 (3H, s), 1.81-1.88 (2H, m), 1.49 (3H, d, J=6.6Hz), m/z=349.

Example 157: Synthesis of S-10

[0457] S-10 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

500MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.66 (1H d, J=6.8Hz), 7.03 (1H, s), 7.01 (1H, d, J=7.8Hz), 6.86-6.89 (1H, m), 4.64 (1H, q, J=6.2Hz), 2.85 (2H, t, J=6.8Hz), 2.55-2.65 (2H, m), 2.30 (3H, s), 2.28 (3H, s), 1.65-1.70 (4H, m), 1.50 (3H, d, J=6.2Hz), m/z=363.

Example 158: Synthesis of S-11

[0458] S-11 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

500MHz-^{1}H-NMR 8.45 (1H, d, J=8.0Hz), 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (2H, d, J=8.3Hz), 7.64 (1H, d, J=7.1Hz), 7.42-7.52 (3H, m), 7.01-7.04 (2H, m), 6.87 (1H, q, J=7.6Hz), 4.62 (1H, q, J=6.5Hz), 2.85 (2H, t, J=7.3Hz), 2.51-2.63 (2H, m), 3.00 (3H, s), 2.29 (3H, s), 1.61-1.68 (2H, m), 1.44-1.57 (4H, m), 1.49 (3H, d, J=6.5Hz), m/z=377.

Example 159: Synthesis of S-12

[0459] S-12 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

500MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.73 (1H, d, J=8.0Hz), 7.64 (1H, d, J=7.1Hz), 7.40-7.52 (3H m), 6.06-6.98 (2H, m), 6.87 (1H, d, J=7.6Hz), 4.62 (1H, q, J=6.6Hz), 2.84 (2H, t, J=7.3Hz), 2.49-2.63 (2H, m), 2.30 (3H, s), 2.29 (3H, s), 1.59-1.67 (2H, m), 1.46-1.55 (2H, m), 1.49 (3H, d, J=6.6Hz), 1.27-1.46 (4H, m), m/z=391.

Example 160: Synthesis of S-13

[0460] S-13 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

500MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.68 (1H, d, J=7.1Hz), 7.41-7.53 (3H, m), 7.04 (1H, s), 7.02 (1H, d, J=7.6Hz), 6.87 (1H, d, J=7.6Hz), 4.66 (1H, q, J=6.5Hz), 2.84 (2H, t, J=7.3Hz), 2.30 (3H, s), 2.29 (3H, s), 1.58-1.66 (2H, m), 1.53 (3H, d, J=6.5Hz), 1.34-1.44 (2H, m), 1.26-1.30 (4H, m), m/z=405.

Example 161: Synthesis of S-14

[0461] S-14 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 419.

Example 162: Synthesis of S-15

[0462] S-15 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.6Hz), 7.83-7.88 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.65 (1H, d, J=6.8Hz), 7.40-7.52 (3H, m), 7.06 (1H, s), 7.03 (1H, d, J=7.6Hz), 6.87 (1H, d, J=7.6Hz), 4.63 (1H, q, J=6.5Hz), 2.86 (2H, t, J=7.3Hz), 2.50-2.62 (2H, m), 2.31 (3H, s), 2.30 (3H, s), 1.60-1.70 (2H, m), 1.49 (3H, d, J=6.5Hz), 1.20-1.50 (14H, m), m/z=447.

Example 163: Synthesis of S-16

[0463] S-16 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.65 (1H, d, J=7.1Hz), 7.46-7.53 (3H, m), 7.06 (1H, s), 7.03 (1H, d, J=7.8Hz), 6.87 (1H, d, J=7.8Hz), 4.63 (1H, q, J=6.6Hz), 2.87 (2H, t, J=7.4Hz), 2.50-2.63 (2H, m), 2.31 (3H, s), 2.30 (3H, s), 1.61-1.69 (2H, m), 1.15-1.55 (18H, m), 1.50 (3H, d, J=6.6Hz), m/z=475.

Example 164: Synthesis of S-17

[0464] S-17 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 2,4-dimethylthiophenol.

400MHz-^{1}H-NMR 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 7.14 (1H, d, J=8.0Hz), 6.98 (1H, s), 6.90-6.92 (1H, m), 6.85-6.88 (2H, m), 6.75-6.81 (1H, m), 3.80 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.93-2.97 (2H, m), 2.62-2.74 (2H, m), 2.34 (3H, s), 2.27 (3H, s), 1.33 (3H, d, J=6.6Hz), m/z=315.

Example 165: Synthesis of S-18

[0465] S-18 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4-dimethylthiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=8.1Hz, J=8.1Hz), 7.16 (1H, d, J=7.8Hz), 6.98 (1H, s), 6.92-6.95 (1H, m), 6.86-6.88 (2H, m), 6.75-6.79 (1H, m), 3.80 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.80-2.93 (2H, m), 2.51-2.65 (2H, m), 2.32 (3H, s), 2.28 (3H, s), 1.70-1.81 (2H, m), 1.32 (3H, d, J=6.6Hz), m/z=329.

Example 166: Synthesis of S-19

[0466] S-19 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4-dimethylthiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.3Hz, J=8.3Hz), 7.16 (1H, d, J=7.8Hz), 6.98 (1H, slike), 6.93-6.95 (1H, m), 6.86-6.88 (2H, m), 6.75-6.79 (1H, m), 3.80 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.81 (2H, t, J=6.9Hz), 2.40-2.54 (2H, m), 2.33 (3H, s), 2.28 (3H, s), 1.53-1.66 (4H, m), 1.33 (3H, d, J=6.6Hz), m/z=343.

Example 167: Synthesis of S-20

[0467] S-20 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4-dimethylthiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.16 (1H, d, J=7.8Hz), 6.98 (1H, s), 6.95 (1H, d, J=8.0Hz), 6.66-6.89 (2H, m), 6.70-6.79 (1H, m), 3.81 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.81 (2H, t, J=7.3Hz), 2.38-2.52 (2H, m), 2.33 (3H, s), 2.28 (3H, s), 1.56-1.64 (2H, m), 1.35-1.50 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=357.

Example 168: Synthesis of S-21

[0468] S-21 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4-dimethylthiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.16 (1H, d, J=7.8Hz), 6.98 (1H, s), 6.93-6.96 (1H, m), 6.87-6.90 (2H, m), 6.75-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.81 (2H, t, J=7.3Hz), 2.38-2.51 (2H, m), 2.34 (3H, s), 2.28 (3H, s), 1.56-1.64 (2H, m), 1.24-1.50 (6H, m), 1.34 (2H, d, J=6.6Hz), m/z=371.

Example 169: Synthesis of S-22

[0469] S-22 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4-dimethylthiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.16 (1H, d, J=7.8Hz), 6.99 (1H, s), 6.93-6.96 (1H, m), 6.87-6.90 (2H, m), 6.73-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.81 (2H, t, J=7.4Hz), 2.37-2.51 (2H, m), 2.34 (3H, s), 2.28 (3H, s), 1.56-1.64 (2H, m), 1.24-1.46 (8H, m), 1.34 (3H, d, J=6.6Hz), m/z=385.

Example 170: Synthesis of S-23

[0470] S-23 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4-dimethylthiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.3Hz, J=8.3Hz), 7.17 (1H, d, J=8.0Hz), 6.99 (1H, s), 6.95 (1H, d, J=8.0Hz), 6.87-6.89 (1H, m), 6.75-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.82 (2H, t, J=7.4Hz), 2.38-2.52 (2H, m), 2.34 (3H, s), 2.28 (3H, s), 1.55-1.64 (2H, m), 1.20-1.50 (10H, m), 1.34 (3H, d, J=6.6Hz), m/z=399.

Example 171: Synthesis of S-24

[0471] S-24 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dimethylthiophenol and

(R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.16Hz), 7.83-7.90 (1H, m), 7.72 (1H, d, J=8.0Hz), 7.63 (1H, d, J=7.3Hz), 7.42-7.52 (3H, m), 7.14 (1H, d, J=7.8Hz), 6.98 (1H, s), 6.87-6.90 (1H, m), 4.61 (1H, q, J=6.5Hz), 3.02 (2H, t, J=8.7Hz), 2.73-2.81 (2H, m), 2.34 (3H, s), 2.27 (3H, s), 1.48 (3H, d, J=6.5Hz), m/z=335.

Example 172: Synthesis of S-25

[0472] S-25 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 349.

Example 173: Synthesis of S-26

[0473] S-26 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.85-7.87 (1H, m), 7.23 (1H, d, J=8.3Hz), 7.64 (1H, d, J=7.1Hz), 7.15 (1H, d, J=7.8Hz), 6.98 (1H, s), 6.93-6.95 (1H, m), 4.62 (1H, q, J=6.6Hz), 2.80 (2H, t, J=7.3Hz), 2.48-2.62 (2H, m), 2.35 (3H, s), 2.27 (3H, s), 1.57-1.63 (2H, m), 1.43-1.53 (2H, m), 1.25-1.44 (4H, m), 1.49 (3H, d, J=6.6Hz), m/z=391.

Example 174: Synthesis of S-27

[0474] S-27 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.87 (1H, d, J=6.0Hz), 7.68-7.78 (2H, m), 7.45-7.55 (3H, m), 7.15 (1H, d, J=7.8Hz), 6.98 (1H, s), 6.94 (1H, d, J=7.8Hz), 4.69 (1H, q, J=6.6Hz), 2.79 (2H, t, J=7.3Hz), 2.50-2.63 (2H, m), 2.33 (3H, s), 2.27 (3H, s), 1.14-1.62 (13H, m), m/z=405.

Example 175: Synthesis of S-28

[0475] S-28 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-α-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.0Hz), 7.86-7.90 (1H, m), 7.70-7.80 (2H, m), 7.45-7.55 (3H, m), 7.16 (1H, d, J=7.8Hz), 6.98 (1H, s), 6.94 (1H, d, J=7.8Hz), 4.72 (1H, q, J=6.4Hz), 2.80 (2H, t, J=7.4Hz), 2.50-2.65 (2H, m), 2.33 (3H, s), 2.27 (3H, s), 1.17-1.63 (15H, m), m/z=419.

Example 176: Synthesis of S-29

[0476] S-29 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 2,6-dimethylthiophenol.

400MHz-^{1}H-NMR 7.21 (1H, dd, J=8.1Hz, J=8.1Hz), 7.05-7.12 (3H, m), 6.83-6.86 (2H, m), 6.73-6.78 (1H, m), 3.80 (3H, s), 3.69 (1H, q, J=6.6Hz), 2.72-2.82 (2H, m), 2.57-2.64 (2H, m), 2.51 (6H, s), 1.32 (3H, d, J=6.6Hz), m/z=315.

Example 177: Synthesis of S-30

[0477] S-30 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,6-dimethylthiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=8.1Hz, J=8.1Hz), 7.05-7.09 (3H, m), 6.84-6.86 (2H m), 6.74-6.78 (1H, m), 3.80 (3H, s), 3.69 (1H, q, J=6.6Hz), 2.62-2.70 (2H, m), 2.51-2.60 (2H, m), 2.50 (6H, s), 1.61-1.70 (2H, m), 1.32 (3H, d,

J=6.6Hz), m/z=329.

Example 178: Synthesis of S-31

[0478] S-31 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,6-dimethylthiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 7.04-7.09 (3H, m), 6.85-6.88 (2H, m), 6.77 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.0Hz), 3.80 (3H, s), 3.70 (1H, q, J=6.6Hz), 2.61 (2H, t, J=6.7Hz), 2.51 (6H, s), 2.39-2.48 (2H, m), 1.48-1.58 (4H, m), 1.32 (3H, d, J=6.6Hz), m/z=343.

Example 179: Synthesis of S-32

[0479] S-32 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,6-dimethylthiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.06-7.11 (1H, m), 6.86-6.88 (2H, m), 6.75-6.79 (1H, m), 3.81 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.61 (2H, t, J=7.3Hz), 2.52 (6H, s), 2.38-2.49 (2H, m), 1.34-1.54 (6H, m), 1.33 (3H, d, J=6.6Hz), m/z=357.

Example 180: Synthesis of S-33

[0480] S-33 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,6-dimethylthiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.07-7.11 (3H, m), 6.86-6.88 (2H, m), 6.75-6.79 (1H, m), 3.81 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.61 (2H, t, J=7.3Hz), 2.52 (6H, s), 2.36-2.50 (2H, m), 1.21-1.54 (8H, m), 1.33 (3H, d, J=6.6Hz), m/z=371.

Example 181: Synthesis of S-34

[0481] S-34 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,6-dimethylthiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.20-7.25 (1H, m), 7.07-7.09 (3H, m), 6.86-6.90 (2H, m), 6.75-6.78 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.61 (2H, t, J=7.32Hz), 2.53 (6H, s), 2.36-2.50 (2H, m), 1.20-1.54 (10H, m), 1.34 (3H, d, J=6.6Hz), m/z=385.

Example 182: Synthesis of S-35

[0482] S-35 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,6-dimethylthiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.20-7.25 (1H, m), 7.05-7.10 (3H, m), 6.88-6.89 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.73 (1H, q, J=6.5Hz), 2.61 (2H, t, J=7.3Hz), 2.53 (6H, s), 2.37-2.49 (2H, m), 1.20-1.55 (12H, m), 1.35 (3H, d, J=6.5Hz), m/z=399.

Example 183: Synthesis of S-36

[0483] S-36 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,6-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.0Hz), 7.83-7.90 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.63 (1H, d, J=7.1Hz), 7.43-7.52 (3H, m), 7.04-7.12 (3H, m), 4.59 (1H, q, J=6.6Hz), 2.77-2.86 (2H, m), 2.70 (2H, t, J=6.6Hz), 2.50 (6H, s), 1.47 (3H, d, J=6.6Hz), m/z=335.

Example 184: Synthesis of S-37

[0484] S-37 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.0Hz), 7.84-7.87 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.62 (1H, d, J=7.1Hz), 7.44-7.51 (3H, m), 7.04-7.11 (3H, m), 4.58 (1H, q, J=6.5Hz), 2.58-2.73 (4H, m), 2.50 (6H, s), 1.68-1.75 (2H, m), 1.47 (3H, d, J=6.5Hz), m/z=349.

Example 185: Synthesis of S-38

[0485] S-38 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.63 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 7.05-7.11 (3H, m), 4.61 (1H, q, J=6.5Hz), 2.61 (2H, t, J=7.3Hz), 2.50-2.59 (2H, m), 2.50 (6H, s), 1.50-1.64 (4H, m), 1.48 (3H, d, J=6.5Hz), m/z=363.

Example 186: Synthesis of S-39

[0486] S-39 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.63 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 7.06-7.08 (3H, m), 4.61 (1H, q, J=6.6Hz), 2.61 (2H, t, J=7.1Hz), 2.50-2.58 (2H, m), 2.51 (6H, s), 1.35-1.55 (6H, m), 1.48 (3H, d, J=6.6Hz), m/z=377.

Example 187: Synthesis of S-40

[0487] S-40 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.87 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.64 (1H, d, J=5.9Hz), 7.44-7.52 (3H, m), 7.05-7.09 (3H, m), 4.62 (1H, q, J=6.5Hz), 2.50-2.62 (4H, m), 2.52 (6H, s), 1.23-1.53 (8H, m), 1.49 (3H, d, J=6.5Hz), m/z=391.

Example 188: Synthesis of S-41

[0488] S-41 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.64 (1H, d, J=7.1Hz), 7.44-7.53 (3H, m), 7.07-7.09 (3H, m), 4.62 (1H, q, J=6.6Hz), 2.50-2.62 (4H, m), 2.52 (6H, s), 1.20-1.53 (10H, m), 1.49 (3H, d, J=6.6Hz), m/z=405.

Example 189: Synthesis of S-42

[0489] S-42 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,6-

dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.6Hz), 7.86-7.89 (1H, m), 7.74-7.78 (2H, m), 7.46-7.54 (3H, m), 6.99-7.10 (3H, m), 4.70-4.78 (1H, m), 2.51-2.62 (4H, m), 2.52 (6H, s), 1.07-1.84 (12H, m), 1.59 (3H, d, J=6.1Hz), m/z=419.

Example 190: Synthesis of S-43

[0490] S-43 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 3,4-dimethylthiophenol.

400MHz-^{1}H-NMR 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 7.11 (1H, s), 7.00-7.07 (2H, m), 6.80-6.87 (2H, m), 6.75-6.87 (2H, m), 6.75-6.78 (1H, m), 3.79 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.95-2.99 (2H, m), 2.63-2.70 (2H, m), 2.21 (3H, s), 2.20 (3H, s), 1.33 (3H, d, J=6.5Hz), m/z=315.

Example 191: Synthesis of S-44

[0491] S-44 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,4-dimethylthiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.20-7.25 (1H, m), 7.12 (1H, s), 7.01-7.08 (2H, m), 6.84-6.88 (2H, m), 6.75-6.78 (1H, m), 3.80 (3H, s), 3.70 (1H, q, J=7.0Hz), 2.83-2.95 (2H, m), 2.50-2.63 (2H, m), 2.22 (3H, s), 2.21 (3H, s), 1.72-1.77 (2H, m), 1.32 (3H, d, J=7.0Hz), m/z=329.

Example 192: Synthesis of S-45

[0492] S-45 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,4-dimethylthiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 7.11 (1H, s), 7.01-7.07 (2H, m), 6.85-6.87 (2H, m), 6.75-6.78 (1H, m), 3.80 (3H, s), 3.70 (1H, q, J=7.0Hz), 2.84 (2H, t, J=7.5Hz), 2.40-2.52 (2H, m), 2.22 (3H, s), 2.21 (3H, s), 1.54-1.65 (4H, m), 1.32 (3H, d, J=7.0Hz), m/z=343.

Example 193: Synthesis of S-46

[0493] S-46 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,4-dimethylthiophenol and 1,5-dibromopentane. m/z = 357.

Example 194: Synthesis of S-47

[0494] S-47 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,4-dimethylthiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.12 (1H, s), 7.02-7.08 (2H, m), 6.86-6.89 (2H, m), 6.75-6.78 (1H, m), 3.81 (3H, s), 3.71 (1H, q, J=7.0Hz), 2.84 (2H, t, J=7.3Hz), 2.38-2.50 (2H, m), 2.23 (3H, s), 2.22 (3H, s), 1.56-1.62 (2H, m), 1.24-1.48 (6H, m), 1.33 (3H, d, J=7.0Hz), m/z=377.

Example 195: Synthesis of S-48

[0495] S-48 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,4-dimethylthiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 7.11 (1H, s), 7.01-7.08 (2H, m), 6.86-6.88 (2H, m), 6.75-6.78 (1H, m), 3.80 (3H, s), 3.71 (1H, q, J=6.5Hz), 2.80 (2H, t, J=7.5Hz), 2.38-2.50 (2H, m), 2.22 (3H, s), 2.21 (3H, s),

1.56-1.62 (2H, m), 1.33-1.45 (4H, m), 1.33 (3H, d, J=6.5Hz), 1.24-1.28 (4H, m), m/z=385.

Example 196: Synthesis of S-49

[0496] S-49 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,4-dimethylthiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.21-7.25 (1H, m), 7.12 (1H, s), 7.02-7.08 (2H, m), 6.87-6.89 (1H, d, J=8.0Hz), 6.87 (1H, s), 6.76-6.78 (1H, m), 3.80 (3H, s), 3.70-3.74 (1H, m), 2.85 (2H, t, J=7.8Hz), 2.38-2.50 (2H, m), 2.22 (3H, s), 2.21 (3H, s), 1.56-1.62 (2H, m), 1.33-1.46 (4H, m), 1.34 (3H, d, J=7.0Hz), 1.25 (6H, bs), m/z=399.

Example 197: Synthesis of S-50

[0497] S-50 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,4-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

Example 198: Synthesis of S-51

[0498] S-51 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.5Hz), 8.85 (1H, d, J=9.0Hz), 7.72 (1H, d, J=8.0Hz), 7.61 (1H, d, J=7.5Hz), 7.43-7.49 (3H, m), 7.11 (1H, s), 6.97-7.07 (2H, m), 4.58 (1H, q, J=6.5Hz), 2.85-2.97 (2H, m), 2.61-2.73 (2H, m), 2.22 (6H, s), 1.76-1.82 (2H, m), 1.46 (3H, d, J=6.5Hz), m/z=349.

Example 199: Synthesis of S-52

[0499] S-52 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.86 (1H, d, J=9.0Hz), 8.18 (1H, d, J=8.5Hz), 7.73 (1H, d, J=8.0Hz), 7.62 (1H, d, J=7.0Hz), 7.44-7.51 (3H, m), 7.11 (1H, s), 7.01-7.07 (2H, m), 4.60 (1H, q, J=6.5Hz), 2.84 (2H, t, J=6.8Hz), 2.50-2.62 (2H, m), 1.60-1.68 (4H, m), 1.47 (3H, d, J=6.5Hz), m/z=363.

Example 200: Synthesis of S-53

[0500] S-53 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.5Hz), 7.86 (1H, dd, J=8.0Hz, J=1.5Hz), 7.73 (1H, d, J=8.0Hz), 7.62 (1H, d, J=7.0Hz), 7.44-7.51 (3H, m), 7.11 (1H, s), 7.01-7.09 (2H, m), 4.60 (1H, q, J=6.5Hz), 2.84 (2H, t, J=7.3Hz), 2.50-2.61 (2H, m), 2.22 (3H, s), 2.24 (3H, s), 1.57-1.63 (2H, m), 1.41-1.53 (4H, m), 1.48 (3H, d, J=6.5Hz), m/z=377.

Example 201: Synthesis of S-54

[0501] S-54 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 391.

Example 202: Synthesis of S-55

[0502] S-55 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,4-

dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.0Hz), 7.86 (1H, d, J=8.0Hz), 7.73 (1H, d, J=8.0Hz), 7.63 (1H, d, J=7.5Hz), 7.39-7.51 (3H, m), 7.11 (1H, s), 7.01-7.07 (2H, m), 4.60 (1H, q, J=6.5Hz), 2.83 (2H, t, J=7.3Hz), 2.49-2.59 (2H, m), 2.22 (3H, s), 2.20 (3H, s), 1.28-1.62 (10H, m), 1.48 (3H, d, J=6.5Hz), m/z=405.

Example 203: Synthesis of S-56

[0503] S-56 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.0Hz), 7.87 (1H, d, J=8.0Hz), 7.74 (1H, d, J=8.0Hz), 7.65 (1H, d, J=7.5Hz), 7.45-7.52 (3H, m), 7.12 (1H, s), 7.02-7.08 (2H, m), 4.63 (1H, q, J=7.0Hz), 2.84 (2H, t, J=7.3Hz), 2.51-2.62 (2H, m), 2.22 (3H, s), 2.21 (3H, s), 1.56-1.62 (2H, m), 1.50 (3H, d, J=7.0Hz), 1.45-1.55 (2H, m), 1.33-1.42 (2H, m), 1.25-1.28 (6H, m), m/z=419.

Example 204: Synthesis of S-57

[0504] S-57 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 3,5-dimethylthiophenol.

400MHz-^{1}H-NMR 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 6.96 (2H, s), 6.88-6.91 (2H, m), 6.82 (1H, s), 6.78-6.80 (1H, m), 3.82 (3H, s), 3.76 (1H, q, J=6.5Hz), 3.01-3.06 (2H, m), 2.69-2.78 (2H, m), 2.28 (6H, s), 1.36 (3H, d, J=6.5Hz), m/z=315.

Example 205: Synthesis of S-58

[0505] S-58 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,5-dimethylthiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 6.93 (2H, s), 6.86-6.88 (2H, m), 6.76-6.78 (2H, m), 3.80 (3H, s), 3.71 (1H, q, J=6.5Hz), 2.86-2.98 (2H, m), 2.51-2.65 (2H, m), 2.27 (6H, s), 1.74-1.81 (2H, m), 1.32 (3H, d, J=6.5Hz), m/z=329.

Example 206: Synthesis of S-59

[0506] S-59 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,5-dimethylthiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=7.5Hz, J=7.5Hz), 6.92 (2H, s), 6.86-6.88 (2H, m), 6.75-6.78 (2H, m), 3.80 (3H, s), 3.71 (1H, q, J=7.0Hz), 2.86 (2H, t, J=7.0Hz), 2.39-2.54 (2H, m), 2.27 (6H, s), 1.55-1.68 (4H, m), 1.33 (3H, d, J=7.0Hz), m/z=343.

Example 207: Synthesis of S-60

[0507] S-60 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,5-dimethylthiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 6.92 (2H, s), 6.86-6.88 (2H, m), 6.75-6.78 (2H, m), 3.81 (3H, m), 3.71 (1H, q, J=7.0Hz), 2.87 (2H, t, J=7.3Hz), 2.39-2.51 (2H, m), 2.27 (6H, s), 1.58-1.65 (2H, m), 1.40-1.49 (4H, m), 1.33 (3H, d, J=7.0Hz), m/z=357.

Example 208: Synthesis of S-61

[0508] S-61 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,5-dimethylthiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.93 (2H, s), 6.86-6.89 (2H, m), 6.76-6.78 (2H, m), 3.81 (3H, s), 3.71 (1H, q, J=6.5Hz), 2.87 (2H, t, J=7.3Hz), 2.39-2.88 (2H, m), 2.27 (6H, s), 1.58-1.65 (2H, m), 1.36-1.49 (4H, m), 1.33 (3H, d, J=6.5Hz), 1.25-1.31 (2H, m), m/z=371.

Example 209: Synthesis of S-62

[0509] S-62 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,5-dimethylthiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.93 (2H, s), 6.86-6.89 (2H, m), 6.75-6.78 (2H, m), 3.81 (3H, s), 3.72 (1H, q, =7.0Hz), 2.87 (2H, t, J=7.5Hz), 2.38-2.51 (2H, m), 2.72 (6H, s), 1.58-1.64 (2H, m), 1.35-1.47 (4H, m), 1.33 (3H, d, J=7.0Hz), 1.25-1.30 (4H, m), m/z=385.

Example 210: Synthesis of S-63

[0510] S-63 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3,5-dimethylthiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 6.91 (2H, s), 6.85-6.88 (2H, m), 6.77 (1H, s), 6.74-6.75 (1H, m), 3.79 (3H, s), 3.71 (1H, q, J=6.5Hz), 2.86 (2H, t, J=7.5Hz), 2.37-2.49 (2H, m), 2.26 (6H, s), 1.57-1.63 (2H, m), 1.34-1.43 (4H, m), 1.32 (3H, d, J=6.5Hz), 1.20-1.30 (6H, m), m/z=399.

Example 211: Synthesis of S-64

[0511] S-64 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,5-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.0Hz), 7.85-7.87 (1H, m), 7.72 (1H, d, J=8.0Hz), 7.63 (1H, d, J=6.5Hz), 7.42-7.52 (3H, m), 6.93 (2H, s), 6.79 (1H, s), 4.62 (1H, q, J=6.5Hz), 3.05 (2H, t, J=6.5Hz), 2.76-2.84 (2H, m), 2.24 (6H, s,), 1.48 (3H, d, J=6.5Hz), m/z=335.

Example 212: Synthesis of S-65

[0512] S-65 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.5Hz), 7.86 (1H, d, J=7.0Hz), 7.24 (1H, d, J=8.5Hz), 7.63 (1H, d, J=6.5Hz), 7.45-7.51 (3H, m), 6.93 (2H, s), 6.78 (1H, s), 4.60 (1H, q, J=6.5Hz), 2.89-3.01 (2H, m), 2.63-2.75 (2H, m), 2.26 (6H, s), 1.79-1.85 (2H, m), 1.48 (3H, d, J=6.5Hz), m/z=349.

Example 213: Synthesis of S-66

[0513] S-66 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.86 (1H, d, J=8.5Hz), 8.18 (1H, d, J=8.0Hz), 7.63 (1H, d, J=7.5Hz), 7.23 (1H, d, J=8.0Hz), 7.44-7.51 (3H, m), 6.92 (2H, s), 6.78 (1H, s), 4.61 (1H, q, J=7.0Hz), 2.86-2.88 (2H, m), 2.53-2.64 (2H, m), 2.26 (6H, s),

1.60-1.70 (4H, m), 1.48 (3H, d, J=7.0Hz), m/z=363.

Example 214: Synthesis of S-67

[0514] S-67 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.85 (1H, d, J=7.5Hz), 8.16 (1H, d, J=8.5Hz), 7.72 (1H, d, J=8.0Hz), 7.61 (1H, d, J=7.5Hz), 7.43-7.50 (3H, m), 6.91 (2H, s), 6.77 (1H, s), 4.60 (1H, q, J=6.5Hz), 2.85 (2H, t, J=7.5Hz), 2.49-2.60 (2H, m), 2.25 (6H, s), 1.58-1.64 (2H, m), 1.41-1.53 (4H, m), 1.47 (3H, d, J=6.5Hz), m/z=377.

Example 215: Synthesis of S-68

[0515] S-68 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.5Hz), 7.86 (1H, d, J=7.5Hz), 7.73 (1H, d, J=8.0Hz), 7.63 (1H, d, J=7.5Hz), 7.46-7.50 (3H, m), 6.92 (2H, s), 6.77 (1H, s), 4.61 (1H, q, J=6.5Hz), 2.86 (2H, t, J=7.3Hz), 2.52-2.61 (2H, m), 2.26 (6H, s), 1.57-1.64 (2H, m), 1.45-1.57 (2H, m), 1.48 (3H, d, J=6.5Hz), 1.35-1.44 (2H, m), 1.29-1.36 (2H, m), m/z=391.

Example 216: Synthesis of S-69

[0516] S-69 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.0Hz), 7.86 (1H, d, J=8.0Hz), 7.73 (1H, d, J=8.0Hz), 7.64 (1H, d, J=7.5Hz), 7.45-7.52 (3H, m), 6.92 (2H, s), 6.78 (1H, s), 4.62 (1H, q, J=7.0Hz), 2.86 (2H, t, J=7.3Hz), 2.51-2.60 (2H, m), 2.27 (6H, s), 1.79-1.85 (2H, m), 1.57-1.63 (2H, m), 1.49 (3H, d, J=7.0Hz), 1.39 (2H, bs), 1.29 (4H, bs), m/z=405.

Example 217: Synthesis of S-70

[0517] S-70 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.5Hz), 7.86 (1H, d, J=8.0Hz), 7.73 (1H, d, J=8.0Hz), 7.64 (1H, d, J=7.5Hz), 7.44-7.52 (3H, m), 6.93 (2H, s), 6.78 (1H, s), 4.62 (1H, q, J=6.5Hz), 2.87 (2H, t, J=7.5Hz), 2.50-2.61 (2H, m), 2.27 (6H, s), 1.58-1.64 (2H, m), 1.47-1.52 (2H, m), 1.49 (3H, d, J=6.5Hz), 1.35-1.42 (2H, m), 1.24-1.30 (6H, m), m/z=419.

Example 218: Synthesis of S-71

[0518] S-71 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 4-bromothiophenol.

40MHz-^{1}H-NMR 7.33-7.37 (2H, m), 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 7.13-7.16 (2H, m), 6.83-6.87 (2H, m), 6.76-6.79 (1H, m), 3.80 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.99 (2H, t, J=6.5Hz), 2.59-2.75 (2H, m), 1.34 (3H, d, J=6.5Hz), m/z=365, 367.

Example 219: Synthesis of S-72

[0519] S-72 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-bromothiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.37 (2H, d, J=8.8Hz), 7.23 (1H, dd, J=8.1Hz, J=8.1Hz), 7.15 (2H, d, J=8.8Hz), 6.85-6.88 (2H, m), 6.78 (1H, ddd, J=8.1Hz, J=2.4Hz, J=1.0Hz), 3.80 (3H, s), 3.71 (1H, q, J=8.2Hz), 2.85-2.98 (2H, m), 2.50-2.65

(2H, m), 1.71-1.81 (2H, m), 1.33 (3H, d, J=6.6Hz), m/z=379, 381.

Example 220: Synthesis of S-73

[0520] S-73 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-bromothiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.37 (2H, d, J=8.5Hz), 7.23 (1H, dd, J=8.1Hz, J=8.1Hz), 7.15 (2H, d, J=8.5Hz), 6.85-6.88 (2H, m), 6.75-6.79 (1H, m), 3.80 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.85 (2H, t, J=7.1Hz), 2.39-2.54 (2H, m), 1.51-1.69 (4H, m), 1.33 (3H, d, J=6.6Hz), m/z=393, 395.

Example 221: Synthesis of S-74

[0521] S-74 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-bromothiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.37 (2H, d, J=8.8Hz), 7.23 (1H, dd, J=8.2Hz, J=8.2Hz), 7.15 (2H, d, J=8.8Hz), 6.86-6.88 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.86 (2H, t, J=7.3Hz), 2.38-2.52 (2H, m), 1.60 (2H, tt, J=7.3Hz, J=7.3Hz), 1.36-1.51 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=407, 409.

Example 222: Synthesis of S-75

[0522] S-75 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-bromothiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.37 (2H, d, J=8.6Hz), 7.23 (1H, dd, J=8.1Hz, J=8.1Hz), 7.15 (2H, d, J=8.6Hz), 6.87-6.89 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.86 (2H, t, J=7.3Hz), 2.38-2.52 (2H, m), 1.60 (2H, tt, J=7.3Hz, J=7.3Hz), 1.23-1.50 (6H, m), 1.35 (3H, d, J=6.6Hz), m/z=421, 423.

Example 223: Synthesis of S-76

[0523] S-76 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-bromothiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.38 (2H, d, J=8.5Hz), 7.23 (1H, dd, J=8.1Hz, J=8.1Hz), 6.87-6.89 (2H, m), 6.78 (1H, ddd, J=8.3Hz, J=2.4Hz, J=1.0Hz), 3.81 (3H, s), 3.73 (1H, q, J=6.6Hz), 2.86 (2H, t, J=7.3Hz), 2.38-2.52 (2H, m), 1.60 (2H, tt, J=7.3Hz, J=7.3Hz), 1.08-1.50 (8H, m), 1.36 (3H, d, J=6.6Hz), m/z=435, 437.

Example 224: Synthesis of S-77

[0524] S-77 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-bromothiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.35-7.40 (2H, m), 7.23 (1H, d, J=8.0Hz), 7.14-7.18 (2H, m), 6.88-6.92 (2H, m), 6.74-6.80 (1H, m), 3.81 (3H, s), 3.75 (1H, q, J=6.7Hz), 2.86 (2H, t, J=7.6Hz), 2.39-2.53 (2H, m), 1.54-1.64 (2H, m), 1.20-1.50 (10H, m), 1.38 (3H, d, J=6.7Hz), m/z=449, 451.

Example 225: Synthesis of S-78

[0525] S-78 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-bromothiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

Example 226: Synthesis of S-79

[0526] S-79 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-bromothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=7.8Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.62 (1H, d, J=6.8Hz), 7.44-7.52 (3H, m), 7.32-7.42 (2H, m), 7.10-7.15 (2H, m), 4.60 (1H, q, J=6.6Hz), 2.83-3.05 (2H, m), 2.60-2.77 (2H, m), 1.76-1.87 (2H, m), 1.49 (3H, d, J=6.6Hz), m/z=399, 401.

Example 227: Synthesis of S-80

[0527] S-80 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-bromothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=7.8Hz), 7.84-7.88 (1H, m), 7.74 (1H, d, J=8.28Hz), 7.62 (1H, d, J=6.6Hz), 7.43-7.52 (3H, m), 7.33-7.37 (2H, m), 7.11-7.16 (2H, m), 4.61 (1H, q, J=6.5Hz), 2.85 (2H, d, J=7.0Hz), 2.50-2.64 (2H, m), 1.58-1.68 (4H, m), 1.48 (3H, d, J=6.5Hz), m/z=413, 415.

Example 228: Synthesis of S-81

[0528] S-81 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-bromothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.2Hz), 7.64 (1H, d, J=7.3Hz), 7.45-7.53 (3H, m), 7.34-7.37 (2H, m), 7.11-7.16 (2H, m), 4.62 (1H, q, J=6.6Hz), 2.85 (2H, t, J=7.3Hz), 2.49-2.62 (2H, m), 1.40-1.65 (6H, m), 1.49 (3H, d, J=6.6Hz), m/z=427, 429.

Example 229: Synthesis of S-82

[0529] S-82 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-bromothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

Example 230: Synthesis of S-83

[0530] S-83 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-bromothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.30 (1H, bs), 8.10 (1H, d, J=8.0Hz), 7.90 (1H, d, J=8.1Hz), 7.82 (1H, d, J=8.1Hz), 7.49-7.59 (3H, m), 7.33-7.38 (2H, m), 7.11-7.15 (2H, m), 4.96 (1H, bs), 2.80 (2H, t, J=7.3Hz), 2.54-2.74 (2H, m), 0.95-1.88 (13H, m), m/z=455, 457.

Example 231: Synthesis of S-84

[0531] S-84 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-bromothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.35 (1H, bs), 8.13 (1H, d, J=8.0Hz), 7.88 (1H, d, J=8.2Hz), 7.79 (1H, d, J=8.3Hz), 7.45-7.56 (3H, m), 7.33-7.39 (2H, m), 7.12-7.18 (2H, m), 4.82 (1H, bs), 2.84 (2H, t, J=7.3Hz), 2.58-2.64 (2H, m), 1.00-1.74 (15H, m), m/z=469, 471.

Example 232: Synthesis of S-85

[0532] S-85 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-iodophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.50-7.54 (2H, m), 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.88 (2H, m), 6.76 (1H, dd, J=8.0Hz, J=2.5Hz), 6.61-6.65 (2H, m), 3.93-4.00 (1H, m), 3.78 (3H, s), 3.72-3.76 (1H, m), 2.58-2.70 (2H, m), 1.86-1.94 (2H,

m), 1.34 (3H, d, J=7.0Hz), m/z=411.

Example 233: Synthesis of S-86

[0533] S-86 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-iodophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.50-7.53 (2H, m), 7.22 (1H, dd, J=3.0Hz, J=3.0Hz), 6.87-6.89 (2H, m), 6.76-6.78 (1H, m), 6.61-6.64 (2H, m), 3.88 (1H, t, J=6.8Hz), 3.80 (3H, s), 3.73 (1H, q, J=6.8Hz), 2.46-2.58 (2H, m), 1.72-1.82 (2H, m), 1.55-1.67 (2H, m), 1.34 (3H, d, J=6.8Hz), m/z=425.

Example 234: Synthesis of S-87

[0534] S-87 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-iodophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.52 (2H, d, J=8.5Hz), 7.20-7.25 (1H, m), 6.87 (2H, s), 6.74-6.80 (1H, m), 6.64 (2H, d, J=8.0Hz), 3.88 (2H, t, J=6.5Hz), 3.80 (3H, s), 3.72 (1H, q, J=6.3Hz), 2.40-2.55 (2H, m), 1.71-1.77 (2H, m), 1.40-1.45 (4H, m), 1.34 (3H, d, J=6.3Hz), m/z=439.

Example 235: Synthesis of S-88

[0535] S-88 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-iodophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.52 (2H, d, J=9.0Hz), 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.89 (2H, m), 6.77 (1H, dd, J=8.0Hz, J=2.0Hz), 6.64 (2H, d, J=9.0Hz), 3.88 (3H, t, J=6.5Hz), 3.81 (3H, s), 3.72 (1H, q, J=7.0Hz), 2.41-2.53 (2H, m), 1.71-1.76 (2H, m), 1.46-4.50 (2H, m), 1.39-1.45 (2H, m), 1.31-1.38 (2H, m), 1.34 (3H, d, J=6.5Hz), m/z=453.

Example 236: Synthesis of S-89

[0536] S-89 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-iodophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.52 (2H, d, J=9.0Hz), 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.89 (2H, m), 6.76-6.78 (1H, m), 6.65 (2H, d, J=8.5Hz), 3.88 (2H, t, J=6.5Hz), 3.81 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.39-2.51 (2H, m), 1.70-1.76 (2H, m), 1.37-1.49 (4H, m), 1.34 (3H, d, J=6.5Hz), 1.25-1.35 (6H, m), m/z=467.

Example 237: Synthesis of S-90

[0537] S-90 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-iodophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.53 (2H, d, J=8.5Hz), 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.89 (2H, m), 6.75-6.78 (1H, m), 6.65 (2H, d, J=8.5Hz), 3.89 (2H, t, J=6.8Hz), 3.81 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.39-2.51 (2H, m), 1.71-1.76 (2H, m), 1.38-1.47 (4H, m), 1.34 (3H, d, J=6.5Hz), 1.25-1.35 (6H, m), m/z=481.

Example 238: Synthesis of S-91

[0538] S-91 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-iodophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17-8.19 (1H, m), 7.84-7.87 (1H, m), 7.73 (1H, d, J=8.0Hz), 7.61 (1H, d, J=7.0Hz), 7.50-7.53 (2H, m), 7.34-7.49 (3H, m), 6.61 (2H, d, J=9.0Hz), 4.63 (1H, q, J=6.5Hz), 3.95-4.01 (2H, m), 2.69-2.80 (2H, m), 1.91-1.97 (2H, m), 1.49 (3H, d, J=6.5Hz), m/z=431.

Example 239: Synthesis of S-92

[0539] S-92 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-iodophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.19 (1H, d, J=7.5Hz), 7.86 (1H, d, J=8.0Hz), 7.73 (1H, d, J=8.0Hz), 7.64 (1H, d, J=8.0Hz), 7.45-7.52 (5H, m), 6.61 (2H, d, J=7.5Hz), 4.63 (1H, q, J=6.5Hz), 3.88 (2H, t, J=6.5Hz), 2.56-2.69 (2H, m), 1.74-1.84 (2H, m), 1.62-1.68 (2H, m), 1.49 (3H, d, J=6.5Hz), m/z=445.

Example 240: Synthesis of S-93

[0540] S-93 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-iodophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.0Hz), 7.86 (1H, d, J=8.5Hz), 7.73 (1H, d, J=8.0Hz), 7.64 (1H, d, J=7.0Hz), 7.45-7.53 (5H, m), 6.63 (2H, d, J=8.5Hz), 4.58-4.64 (1H, m), 3.85-3.88 (2H, m), 2.50-2.65 (2H, m), 1.70-1.76 (2H, m), 1.40-1.55 (4H, m), 1.49 (3H, d, J=6.5Hz), m/z=459.

Example 241: Synthesis of S-94

[0541] S-94 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-iodophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.5Hz), 7.83 (1H, d, J=7.0Hz), 7.72 (1H, d, J=7.5Hz), 7.64 (1H, d, J=7.5Hz), 7.40-7.53 (5H, m), 6.63 (2H, d, J=9.5Hz), 4.62 (1H, q, J=6.5Hz), 3.87 (2H, t, J=6.5Hz), 2.50-2.62 (2H, m), 1.70-1.75 (2H, m), 1.35-1.60 (6H, m), 1.49 (3H, d, J=6.5Hz), m/z=473.

Example 242: Synthesis of S-95

[0542] S-95 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-iodophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.5Hz), 7.87 (1H, d, J=8.0Hz), 7.74 (1H, d, J=7.5Hz), 7.67 (1H, d, J=7.0Hz), 7.45-7.53 (5H, m), 6.64 (2H, d, J=8.5Hz), 4.65 (1H, q, J=7.0Hz), 3.87 (2H, t, J=6.8Hz), 2.51-2.63 (2H, m), 1.78-1.84 (2H, m), 1.69-1.75 (2H, m), 1.52 (3H, d, J=7.0Hz), 1.25-1.45 (6H, m), m/z=487.

Example 243: Synthesis of S-96

[0543] S-96 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-iodophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.86 (1H, d, J=7.5Hz), 8.18 (1H, d, J=8.5Hz), 7.74 (1H, d, J=8.0Hz), 7.66 (1H, d, J=7.5Hz), 7.45-7.54 (5H, m), 6.65 (2H, d, J=8.5Hz), 4.64 (1H, q, J=6.5Hz), 3.88 (2H, t, J=6.8Hz), 2.51-2.63 (2H, m), 1.79-1.85 (2H, m), 1.70-1.75 (2H, m), 1.51 (3H, d, J=6.5Hz), 1.24-1.43 (8H, m), m/z=501.

Example 244: Synthesis of S-97

[0544] S-97 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 2-napthalenethiol. m/z = 337.

Example 245: Synthesis of S-98

[0545] S-98 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing

the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-naphthalenethiol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.75-7.77 (1H, m), 7.69-7.73 (3H, m), 7.37-7.48 (3H, m), 7.21 (1H, dd, J=8.2Hz, J=8.2Hz), 6.85-6.88 (2H, m), 6.75-6.79 (1H, m), 3.79 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.98-3.11 (2H, m), 2.54-2.68 (2H, m), 1.78-1.87 (2H, m), 1.32 (3H, d, J=6.6Hz), m/z=351.

Example 246: Synthesis of S-99

[0546] S-99 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-naphthalenethiol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.69-7.78 (4H, m), 7.38-7.51 (3H, m), 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 6.85-6.88 (2H, m), 6.76 (1H, ddd, J=8.3Hz, J=2.4Hz, J=1.0Hz), 3.79 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.99 (2H, t, J=7.1Hz), 2.41-2.55 (2H, m), 1.56-1.74 (4H, m), 1.33 (3H, d, J=6.6Hz), m/z=365.

Example 247: Synthesis of S-100

[0547] S-100 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-naphthalenethiol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.69-7.78 (4H, m), 7.37-7.51 (3H, m), 7.22 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.88 (2H, m), 6.77 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.0Hz), 3.80 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.99 (2H, t, J=7.3Hz), 2.39-2.52 (2H, m), 1.67 (2H, tt, J=7.3Hz, J=7.3Hz), 1.41-1.53 (4H, m), 1.33 (3H, d, J=6.6Hz), m/z=379.

Example 248: Synthesis of S-101

[0548] S-101 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-naphthalenethiol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.70-7.78 (4H, m), 7.38-7.47 (3H, m), 7.23 (1H, dd, J=8.3Hz, J=8.3Hz), 6.86-6.88 (2H, m), 6.77 (1H, ddd, J=8.3Hz, J=2.4Hz, J=1.0Hz), 3.80 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.99 (2H, t, J=7.3Hz), 2.37-2.51 (2H, m), 1.67 (2H, tt, J=7.3Hz, J=7.3Hz), 1.39-1.50 (4H, m), 1.25-1.35 (2H, m), 1.33 (3H, d, J=6.6Hz), m/z=393.

Example 249: Synthesis of S-102

[0549] S-102 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-naphthalenethiol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.70-7.78 (4H, m), 7.38-7.47 (3H, m), 7.24 (1H, dd, J=8.1Hz, J=8.1Hz), 6.90-6.95 (2H, m), 6.78-6.81 (1H, m), 3.81 (3H, s), 3.79-3.82 (1H, m), 2.99 (2H, t, J=7.4Hz), 2.41-2.54 (2H, m), 1.66 (2H, tt, J=7.4Hz, J=7.4Hz), 1.15-1.55 (8H, m), 1.43 (3H, d, J=6.6Hz), m/z=407.

Example 250: Synthesis of S-103

[0550] S-103 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-naphthalenethiol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.70-7.78 (4H, m), 7.38-7.47 (3H, m), 7.23 (1H, d, J=7.8Hz), 6.88-6.92 (2H, m), 6.78 (1H, ddd, J=8.3Hz, J=2.7Hz, J=1.0Hz), 3.81 (3H, s), 3.76 (1H, q, J=6.4Hz), 2.99 (2H, t, J=7.3Hz), 2.39-2.52 (2H, m), 1.66 (2H, tt, J=7.3Hz, J=7.3Hz), 1.15-1.55 (10H, m), m/z=421.

Example 251: Synthesis of S-104

[0551] S-104 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-naphthalenethiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 357.

Example 252: Synthesis of S-105

[0552] S-105 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-naphthalenethiol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.14-8.16 (1H, m), 7.84-7.88 (1H, m), 7.75-7.77 (2H, m), 7.68-7.76 (3H, m), 7.64 (1H, d, J=6.6Hz), 7.36-7.48 (6H, m), 4.61 (1H, q, J=6.6Hz), 3.00-3.14 (2H, m), 2.66-2.79 (2H, m), 1.88 (2H, m), 1.49 (3H, d, J=6.6Hz), m/z=371.

Example 253: Synthesis of S-106

[0553] S-106 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-naphthalenethiol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.1Hz), 7.84-7.87 (1H, m), 7.74-7.77 (2H, m), 7.68-7.72 (3H, m), 7.63 (1H, d, J=7.1Hz), 7.36-7.51 (6H, m), 4.62 (1H, q, J=6.6Hz), 2.98 (2H, t, J=7.0Hz), 2.52-2.65 (2H, m), 1.63-1.76 (4H, m), 1.48 (3H, d, J=6.6Hz), m/z=385.

Example 254: Synthesis of S-107

[0554] S-107 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-naphthalenethiol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

Example 255: Synthesis of S-108

[0555] S-108 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-naphthalenethiol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74-7.77 (2H, m), 7.69-7.73 (3H, m), 7.64 (1H, d, J=7.1Hz), 7.38-7.52 (6H, m), 4.62 (1H, q, J=6.5Hz), 2.98 (2H, t, J=7.4Hz), 2.49-2.62 (2H, m), 1.66 (2H, tt, J=7.4Hz, J=7.4Hz), 1.27-1.54 (6H, m), 1.49 (3H, d, J=6.5Hz), m/z=413.

Example 256: Synthesis of S-109

[0556] S-109 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-naphthalenethiol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, m), 7.84-7.87 (1H, m), 7.69-7.77 (5H, m), 7.64 (1H, d, J=6.8Hz), 7.37-7.53 (6H, m), 4.62 (1H, q, J=6.6Hz), 2.98 (2H, t, J=7.4Hz), 2.48-2.62 (2H, m), 1.65 (2H, tt, J=7.4Hz, J=7.4Hz), 1.25-1.52 (8H, m), 1.49 (3H, d, J=6.6Hz), m/z=427.

Example 257: Synthesis of S-110

[0557] S-110 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-naphthalenethiol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.14 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.67-7.79 (6H, m), 7.37-7.53 (6H, m), 4.70 (1H, q, J=6.6Hz), 2.98 (2H, t, J=7.3Hz), 2.50-2.65 (2H, m), 1.65 (2H, tt, J=7.3Hz, J=7.3Hz), 1.05-1.60 (10H, m), 1.57 (3H, d, J=6.6Hz), m/z=441.

Example 258: Synthesis of S-111

[0558] S-111 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 2-methoxythiophenol.

400MHz-^{1}H-NMR 7.14-7.22 (3H, m), 6.81-6.89 (4H, m), 6.73-6.76 (1H, m), 3.85 (3H, s), 3.78 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.98 (2H, t, J=6.5Hz), 2.61-2.73 (2H, m), 1.32 (3H, d, J=6.6Hz), m/z=317.

Example 259: Synthesis of S-112

[0559] S-112 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-methoxythiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.21-7.25 (2H, m), 7.14-7.19 (1H, m), 6.82-6.92 (4H, m), 6.77 (1H, ddd, J=8.3Hz, J=2.4Hz, J=1.0Hz), 3.87 (3H, s), 3.80 (3H, s), 3.73 (1H, q, J=6.6Hz), 2.85-2.98 (2H, m), 2.52-2.67 (2H, m), 1.73-1.86 (2H, m), 1.33 (3H, d, J=6.6Hz), m/z=331.

Example 260: Synthesis of S-113

[0560] S-113 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-methoxythiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.21-7.25 (2H, m), 7.14-7.19 (1H, m), 6.82-6.93 (4H, m), 6.75-6.79 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.0Hz), 3.88 (3H, s), 3.80 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.86 (2H, t, J=7.0Hz), 2.41-2.55 (2H, m), 1.58-1.71 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=345.

Example 261: Synthesis of S-114

[0561] S-114 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-methoxythiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.21-7.26 (2H, m), 7.13-7.18 (1H, m), 6.82-6.93 (4H, m), 6.76-6.79 (1H, m), 3.88 (3H, s), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.86 (2H, t, J=7.4Hz), 2.38-2.52 (2H, m), 1.56-1.67 (2H, m), 1.38-1.53 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=359.

Example 262: Synthesis of S-115

[0562] S-115 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-methoxythiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.19-7.24 (2H, m), 7.12-7.16 (1H, m), 6.81-6.91 (4H, m), 6.74-6.77 (1H, m), 3.86 (3H, s), 3.79 (3H, s), 3.70 (1H, q, J=6.6Hz), 2.84 (2H, t, J=7.5Hz), 2.36-2.50 (2H, m), 1.57-1.65 (2H, m), 1.23-1.48 (6H, m), 1.32 (3H, d, J=6.6Hz), m/z=373.

Example 263: Synthesis of S-116

[0563] S-116 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-methoxythiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.21-7.27 (2H, m), 7.13-7.18 (1H, m), 6.89-6.97 (4H, m), 6.80-6.85 (1H, m), 3.88 (3H, s), 3.83 (3H, s), 3.80-3.83 (2H, t, J=7.3Hz), 2.85 (1H, m), 2.43-2.56 (2H, m), 1.36-1.66 (6H, m), 1.47 (3H, d, J=6.2Hz), 1.18-1.30 (4H, m), m/z=387.

Example 264: Synthesis of S-117

[0564] S-117 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-methoxythiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.21-7.25 (2H, m), 7.13-7.18 (1H, m), 6.82-6.94 (4H, m), 6.76-6.79 (1H, m), 3.88 (3H, s), 3.81 (3H, s), 3.73 (2H, t, J=7.3Hz), 2.86 (1H, q, J=6.5Hz), 2.38-2.52 (2H, m), 1.60-1.70 (2H, m), 1.20-1.60 (10H, m), 1.35 (3H, d, J=6.5Hz), m/z=401.

Example 265: Synthesis of S-118

[0565] S-118 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-methoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=7.6Hz), 7.84-7.87 (1H, m), 7.73 (1H, d, J=8.0Hz), 7.64 (1H, d, J=6.4Hz), 7.40-7.51 (3H, m), 7.24 (1H, dd, J=7.6Hz, J=1.7Hz), 7.18 (1H, ddd, J=7.8Hz, J=7.8Hz, J=1.7Hz), 6.81-6.88 (2H, m), 4.62 (1H, q, J=6.6Hz), 3.84 (3H, s), 3.05 (2H, t, J=6.4Hz), 2.73-2.82 (2H, m), 1.48 (3H, d, J=6.6Hz), m/z=337.

Example 266: Synthesis of S-119

[0566] S-119 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-methoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=7.6Hz), 7.82-7.86 (1H, m), 7.72 (1H, d, J=8.3Hz), 7.63 (1H, d, J=6.8Hz), 7.43-7.50 (3H, m), 7.21 (1H, dd, J=7.6Hz, J=1.5Hz), 7.14 (1H, ddd, J=8.0HZ, J=8.0Hz, J=1.5Hz), 6.87 (1H, dd, J=7.6Hz, J=1.2Hz), 6.81 (1H, dd, J=8.0Hz, J=1.1Hz), 4.61 (1H, q, J=6.6Hz), 3.84 (3H, s), 2.85-2.99 (2H, m), 2.61-2.77 (2H, m), 1.78-1.86 (2H, m), 1.47 (3H, d, J=6.6Hz), m/z=351.

Example 267: Synthesis of S-120

[0567] S-120 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-methoxythiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.64 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 7.21 (1H, dd, J=7.8Hz, J=1.6Hz), 7.13-7.18 (1H, m), 6.89 (ddd, J=7.6Hz, J=7.6Hz, J=1.2Hz), 6.82 (1H, dd, J=8.3Hz, J=1.2Hz), 4.62 (1H, q, J=6.5Hz), 3.86 (3H, s), 2.83-2.88 (2H, m), 2.52-2.65 (2H, m), 1.64-1.70 (4H, m), 1.49 (3H, d, J=6.5Hz), m/z=365.

Example 268: Synthesis of S-121

[0568] S-121 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-methoxythiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.83-7.88 (1H, m), 7.71-7.75 (1H, m), 7.63 (1H, d, J=7.0Hz), 7.41-7.52 (3H, m), 7.21 (1H, dd, J=7.6Hz, J=1.7Hz), 7.15 (1H, ddd, J=7.6Hz, J=7.6Hz, J=1.7Hz), 6.90 (1H, ddd, J=7.6Hz, J=7.6Hz, J=1.2Hz), 6.82 (1H, dd, J=8.2Hz, J=1.1Hz), 4.61 (1H, q, J=6.6Hz), 3.87 (3H, s), 2.85 (2H, t, J=7.3Hz), 2.50-2.62 (2H, m), 1.40-1.48 (6H, m), 1.49 (3H, d, J=6.6Hz), m/z=379.

Example 269: Synthesis of S-122

[0569] S-122 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-methoxythiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 393.

Example 270: Synthesis of S-123

[0570] S-123 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-methoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.87 (1H, d, J=7.1Hz), 7.70-7.78 (2H, m), 7.41-7.51 (3H, m), 7.21 (1H, dd, J=7.6Hz, J=1.5Hz), 7.12-7.17 (1H, m), 6.90 (1H, ddd, J=7.6Hz, J=7.6Hz, J=1.2Hz), 6.80-6.83 (1H, m), 4.67-4.75 (1H, m), 3.87 (3H, s), 2.84 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.05-1.64 (13H, m), m/z=407.

Example 271 : Synthesis of S-124

[0571] S-124 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-methoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 7.86-7.89 (1H, m), 7.70-7.78 (2H, m), 7.46-7.55 (3H, m), 7.22 (1H, dd, J=7.6Hz, J=1.7Hz), 7.13-7.17 (1H, m), 6.87-6.92 (1H, m), 4.70 (1H, bs), 3.88 (3H, s), 2.85 (2H, t, J=7.4Hz), 2.52-2.64 (2H, m), 1.05-1.65 (15H, m), m/z=421.

Example 272: Synthesis of S-125

[0572] S-125 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiol by 3-methoxythiophenol.

400MHz-^{1}H-NMR 7.22 (1H, d, J=8.0Hz), 7.16 (1H, dd, J=8.0Hz, J=8.0Hz), 6.83-6.89 (4H, m), 6.77 (1H, ddd, J=8.0Hz, J=2.6Hz, J=1.0Hz), 6.71 (1H, ddd, J=7.5Hz, J=2.6Hz, J=1.0Hz), 3.80 (3H, s), 3.78 (3H, s), 3.74 (1H, q, J=6.5Hz), 3.02-3.06 (2H, m), 2.67-2.78 (2H, m), 1.35 (3H, d, J=6.5Hz), m/z=317.

Example 273: Synthesis of S-126

[0573] S-126 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3-methoxythiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.18 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.89 (3H, m), 6.85 (1H, dd, J=2.1Hz, J=2.1Hz), 6.78 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.2Hz), 6.70 (1H, ddd, J=8.4Hz, J=2.7Hz, J=1.0Hz), 3.81 (3H, s), 3.78 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.88-3.02 (2H, m), 2.51-2.66 (2H, m), 1.74-1.87 (2H, m), 1.33 (3H, d, J=6.6Hz), m/z=331.

Example 274: Synthesis of S-127

[0574] S-127 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3-methoxythiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.18 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.89 (3H, m), 6.83-6.84 (1H, m), 6.76-6.79 (1H, m), 6.69 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.0Hz), 3.81 (3H, s), 3.79 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.89 (2H, t, J=7.1Hz), 2.40-2.55 (2H, m), 1.53-1.72 (4H, m), 1.34 (4H, m), m/z=345.

Example 275: Synthesis of S-128

[0575] S-128 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3-methoxythiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.18 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.89 (3H, m), 6.84 (1H, dd, J=4.1Hz, J=4.1Hz), 6.76-6.79 (1H, m), 6.70 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.0Hz), 3.81 (3H, s), 3.79 (3H, s), 3.72 (1H, q, J=6.5Hz), 2.89 (2H, t, J=7.3Hz), 2.38-2.52 (2H, m), 1.59-1.67 (2H, m), 1.37-1.52 (4H, m), 1.34 (3H, d,

J=6.5Hz), m/z=359.

Example 276: Synthesis of S-129

[0576] S-129 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3-methoxythiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 7.18 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.90 (3H, m), 6.83-6.85 (1H, m), 6.76-6.79 (1H, m), 6.69 (1H, ddd, J=8.3Hz, J=2.6Hz, J=1.0Hz), 3.81 (3H, s), 3.79 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.89 (2H, t, J=7.3Hz), 2.37-2.51 (2H, m), 1.59-1.67 (2H, m), 1.24-1.52 (6H, m), 1.35 (3H, d, J=6.6Hz), m/z=373.

Example 277: Synthesis of S-130

[0577] S-130 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3-methoxythiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 7.18 (1H, dd, J=8.0Hz, =8.0Hz), 6.86-6.90 (3H, m), 6.76-6.80 (1H, m), 6.69 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.0Hz), 3.81 (3H, s), 3.79 (3H, s), 3.74 (1H, q, J=6.6Hz), 2.89 (2H, t, J=7.3Hz), 2.38-2.52 (2H, m), 1.58-1.66 (2H, m), 1.19-1.49 (8H, m), 1.37 (3H, d, J=6.6Hz), m/z=387.

Example 278: Synthesis of S-131

[0578] S-131 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 3-methoxythiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, =8.0Hz), 7.18 (1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.91 (3H, m), 6.84-6.85 (1H, m), 6.78 (1H, ddd, J=8.0Hz, J=2.4Hz, J=0.8Hz), 6.69 (1H, ddd, J=8.0Hz, J=2.4Hz, J=0.8Hz), 3.81 (3H, s), 3.79 (3H, s), 3.73 (1H, q, J=6.5Hz), 2.89 (2H, t, J=7.4Hz), 2.38-2.52 (2H, m), 1.59-1.70 (2H, m), 1.20-1.50 (10H, m), 1.35 (3H, d, J=6.5Hz), m/z=401.

Example 279: Synthesis of S-132

[0579] S-132 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3-methoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=7.8Hz), 7.85-7.87 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.63 (1H, d, J=6.6Hz), 7.42-7.55 (3H, m), 7.12-7.16 (1H, m), 6.85-6.89 (2H, m), 6.69-6.72 (1H, m), 4.63 (1H, q, J=6.5Hz), 3.76 (1H, s), 3.08 (2H, t, J=6.4Hz), 2.76-2.87 (2H, m), 1.49 (3H, d, J=6.5Hz), m/z=337.

Example 280: Synthesis of S-133

[0580] S-133 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3-methoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=9.4Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.63 (1H, d, J=6.6Hz), 7.44-7.52 (3H, m), 7.16 (1H, dd, J=7.8Hz, J=7.8Hz), 6.84-6.89 (2H, m), 6.68-6.71 (1H, m), 4.61 (1H, q, J=6.6Hz), 3.77 (3H, s), 2.91-3.04 (2H, m), 2.62-2.76 (2H, m), 1.80-1.90 (2H, m), 1.48 (3H, d, J=6.6Hz), m/z=351.

Example 281: Synthesis of S-134

[0581] S-134 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3-methoxythiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.73 (1H, d, J=8.0Hz), 7.63 (1H, d, J=6.84Hz), 7.44-7.52 (3H, m), 7.16 (1H, dd, J=7.8Hz, J=7.8Hz), 6.83-6.88 (2H, m), 6.67-6.70 (1H, m), 4.62 (1H, q, J=6.6Hz), 3.77 (3H, s), 2.89 (2H, t, J=7.1Hz), 2.51-2.65 (2H, m), 1.59-1.73 (4H, m), 1.49 (3H, d, J=6.6Hz), m/z=365.

Example 282: Synthesis of S-135

[0582] S-135 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3-methoxythiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.1Hz), 7.63 (1H, d, J=6.6Hz), 7.43-7.52 (3H, m), 7.17 (1H, dd, J=8.0Hz, J=8.0Hz, 6.85-6.88 (1H, m), 6.84 (1H, dd, J=2.1Hz, J=2.1Hz), 6.69 (1H, ddd, J=6.7Hz, J=2.4Hz, J=0.7Hz), 4.62 (1H, q, J=6.6Hz), 3.78 (3H, s), 2.88 (2H, t, J=7.3Hz), 2.50-2.63 (2H, m), 1.59-1.67 (2H, m), 1.40-1.55 (4H, m), 1.49 (3H, d, J=6.6Hz), m/z=379.

Example 283: Synthesis of S-136

[0583] S-136 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3-methoxythiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 7.80-7.88 (2H, m), 7.73-7.76 (1H, m), 7.41-7.53 (3H, m), 6.85-6.88 (1H, m), 6.83 (1H, dd, J=2.1Hz, J=2.1Hz), 6.68 (1H, ddd, J=8.4Hz, J=2.4Hz, J=0.9Hz), 4.67 (1H, q, J=6.6Hz), 2.87 (2H, t, J=7.3Hz), 2.51-2.63 (2H, m), 1.25-1.66 (11H, m), m/z=393.

Example 284: Synthesis of S-137

[0584] S-137 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3-methoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.86-7.89 (1H, m), 7.75-7.80 (2H, m), 7.45-7.55 (3H, m), 7.16 (1H, dd, J=8.1Hz, J=8.1Hz), 6.82-6.88 (2H, m), 6.68 (1H, ddd, J=8.3Hz, J=2.4Hz, J=0.7Hz), 4.70-4.78 (1H, m), 3.78 (3H, s), 2.86 (2H, t, J=7.3Hz), 2.52-2.65 (2H, m), 1.05-1.65 (13H, m), m/z=407.

Example 285: Synthesis of S-138

[0585] S-138 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 3-methoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.14 (1H, d, J=8.0Hz), 7.87-7.89 (1H, m), 7.77 (1H, d, J=8.0Hz), 7.47-7.55 (3H, m), 7.17 (1H, dd, J=8.1Hz, J=8.1Hz), 6.83-6.89 (2H, m), 6.68 (1H, ddd, J=8.3Hz, J=2.4Hz, J=1.0Hz), 4.75 (1H, bs), 3.78 (3H, s), 2.88 (2H, t, J=7.3Hz), 2.53-2.66 (2H, m), 1.00-1.75 (15H, m), m/z=421.

Example 286: Synthesis of S-139

[0586] S-139 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiol by 4-methoxythiophenol.

400MHz-^{1}H-NMR 7.28 (2H, d, J=8.0Hz), 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 6.75-6.88 (5H, m), 3.80 (3H, s), 3.78 (3H, s), 3.70 (1H, q, J=6.6Hz), 2.88-2.93 (2H, m), 2.57-2.70 (2H, m), 1.34 (3H, d, J=6.6Hz), m/z=317.

Example 287: Synthesis of S-140

[0587] S-140 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-methoxythiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.31 (2H, d, J=8.8Hz), 7.23 (1H, dd, J=8.1Hz, J=8.1Hz), 6.85-6.88 (2H, m), 6.82 (2H, d, J=8.8Hz), 6.77 (1H, ddd, J=8.2Hz, J=2.7Hz, J=1.0Hz), 3.80 (3H, s), 3.79 (3H, s), 3.70 (1H, q, J=6.6Hz), 2.77-2.89 (2H, m), 2.49-2.64 (2H, m), 1.64-1.80 (2H, m), 1.32 (3H, d, J=6.6Hz), m/z=331.

Example 288: Synthesis of S-141

[0588] S-141 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-methoxythiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.31 (2H, d, J=8.8Hz), 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.85-6.89 (2H, m), 6.82 (2H, d, J=8.8Hz), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.75-2.80 (2H, m), 2.33-2.53 (2H, m), 1.53-1.62 (4H, m), 1.33 (3H, d, J=6.6Hz), m/z=345.

Example 289: Synthesis of S-142

[0589] S-142 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-methoxythiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.31 (2H, d, J=8.8Hz), 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.89 (2H, m), 6.83 (2H, d, J=8.8Hz), 6.76-6.80 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.71 (1H, q, J=6.6Hz), 2.78 (2H, t, J=7.3Hz), 2.38-2.52 (2H, m), 1.50-1.60 (2H, m), 1.36-1.50 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=359.

Example 290: Synthesis of S-143

[0590] S-143 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-methoxythiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.31 (2H, d, J=8.8Hz), 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.90 (2H, m), 6.81-6.85 (2H, m), 6.76-6.80 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.73 (1H, q, J=6.6Hz), 2.78 (2H, t, J=7.3Hz), 2.38-2.51 (2H, m), 1.21-1.59 (8H, m), 1.35 (3H, d, J=6.6Hz), m/z=373.

Example 291: Synthesis of S-144

[0591] S-144 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-methoxythiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.32 (2H, d, J=8.8Hz), 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 6.88-6.91 (2H, m), 6.83 (2H, d, J=8.8Hz), 6.76-6.80 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.75 (1H, q, J=6.6Hz), 2.78 (2H, t, J=7.4Hz), 2.38-2.52 (2H, m), 1.40-1.60 (4H, m), 1.20-1.30 (4H, m), 1.32-1.40 (2H, m), 1.37 (3H, d, J=6.6Hz), m/z=387.

Example 292: Synthesis of S-145

[0592] S-145 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-methoxythiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.29-7.33 (2H, m), 7.25 (1H, dd, J=8.0Hz, J=8.0Hz), 6.92-6.99 (2H, m), 6.79-6.85 (2H, m), 3.83 (3H, s), 3.79 (3H, s), 3.81-3.84 (1H, m), 2.78 (2H, t, J=7.4Hz), 2.43-2.56 (2H, m), 1.43-1.60 (4H, m), 1.19-1.40 (8H, m), 1.48 (3H, d, J=5.9Hz), m/z=401.

Example 293: Synthesis of S-146

[0593] S-146 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=7.6Hz), 7.85-7.89 (1H, m), 7.73 (1H, d, J=8.2Hz), 7.62 (1H, d, J=6.6Hz), 7.42-

7.52 (3H, m), 7.27-7.30 (2H, m), 6.75-6.80 (2H, m), 4.61 (1H, q, J=6.5Hz), 3.78 (3H, s), 2.97 (2H, t, J=6.2Hz), 2.68-2.78 (2H, m), 1.48 (3H, d, J=6.5Hz), m/z=337.

Example 294: Synthesis of S-147

[0594] S-147 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=7.8Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.64 (1H, d, J=7.1Hz), 7.46-7.52 (3H, m), 7.27-7.31 (2H, m), 6.77-6.82 (2H, m), 4.61 (1H, q, J=6.5Hz), 3.78 (3H, s), 2.79-2.92 (2H, m), 2.61-2.75 (2H, m), 1.73-1.81 (2H, m), 1.49 (3H, d, J=6.5Hz), m/z=351.

Example 295: Synthesis of S-148

[0595] S-148 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methoxythiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.64 (1H, d, J=6.4Hz), 7.45-7.53 (3H, m), 7.28-7.31 (2H, m), 6.78-6.82 (2H, m), 4.62 (1H, q, J=6.4Hz), 3.78 (3H, s), 2.78 (2H, t, J=6.7Hz), 2.49-2.63 (2H, m), 1.46-1.68 (4H, m), 1.49 (3H, d, J=6.4Hz), m/z=365.

Example 296: Synthesis of S-149

[0596] S-149 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methoxythiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.83-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.63 (1H, d, J=7.1Hz), 7.46-7.53 (3H, m), 7.28-7.32 (2H, m), 6.79-6.83 (2H, m), 4.62 (1H, q, J=6.6Hz), 3.78 (3H, s), 2.78 (2H, t, J=7.3Hz), 2.48-2.61 (2H, m), 1.46-1.60 (4H, m), 1.49 (3H, d, J=6.6Hz), 1.36-1.44 (2H, m), m/z=379.

Example 297: Synthesis of S-150

[0597] S-150 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methoxythiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.82-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.65 (1H, d, J=7.1 Hz), 7.41-7.54 (3H, m), 7.28-7.33 (2H, m), 6.80-6.84 (2H, m), 4.63 (1H, q, J=6.4Hz), 3.78 (3H, s), 2.75-2.79 (2H, m), 2.49-2.61 (2H, m), 1.24-1.58 (8H, m), m/z=393.

Example 298: Synthesis of S-151

[0598] S-151 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.0Hz), 7.86-7.88 (1H, m), 7.71-7.77 (2H, m), 7.46-7.54 (3H, m), 7.29-7.32 (2H, m), 6.80-6.84 (2H, m), 4.69 (1H, bs), 3.80 (3H, s), 2.77 (2H, t, J=7.5Hz), 2.51-2.64 (2H, m), 1.00-1.64 (13H, m), m/z=407.

Example 299: Synthesis of S-152

[0599] S-152 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.0Hz), 7.86-7.89 (1H, m), 7.71-7.77 (2H, m), 7.45-7.54 (3H, m), 7.29-7.33 (2H, m), 6.80-6.85 (2H, m), 4.66-4.76 (1H, m), 3.78 (3H, s), 2.78 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.05-1.56 (15H, m), m/z=421.

Example 300: Synthesis of S-153

[0600] S-153 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiol by 2,3,5,6-tetrafluorothiophenol.

400MHz-^{1}H-NMR 7.21 (1H, dd, J=8.0Hz, J=8.0Hz), 6.96-7.06 (1H, m), 6.82-6.86 (2H, m), 6.74-6.77 (1H, m), 3.80 (3H, s), 3.70 (1H, q, J=6.6Hz), 3.03 (2H, t, J=6.0Hz), 2.55-2.67 (2H, m), 1.34 (3H, d, J=6.6Hz), m/z=359.

Example 301: Synthesis of S-154

[0601] S-154 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrafluorothiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.3Hz, J=8.3Hz), 6.97-7.06 (1H, m), 6.84-6.87 (2H, m), 6.74-6.79 (1H, m), 3.81 (3H, s), 3.70 (1H, q, J=6.6Hz), 2.90-3.03 (2H, m), 2.49-2.65 (2H, m), 1.66-1.75 (2H, m), 1.33 (3H, d, J=6.6Hz), m/z=373.

Example 302: Synthesis of S-155

[0602] S-155 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrafluorothiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.1Hz.J=8.1Hz), 6.97-7.06 (1H, m), 6.84-6.88 (2H, m), 6.76-6.78 (1H, m), 3.81 (3H, s), 3.70 (1H, q, J=6.6Hz), 2.91 (2H, t, J=6.6Hz), 2.37-2.53 (2H, m), 1.53-1.63 (4H, m), 1.32 (3H, d, J=6.6Hz), m/z=387.

Example 303: Synthesis of S-156

[0603] S-156 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrafluorothiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.96-7.05 (1H, m), 6.85-6.89 (2H, m), 6.75-6.79 (1H, m), 3.81 (3H, s), 3.71 (1H, q, J=6.5Hz), 2.91 (2H, t, J=7.3Hz), 2.37-2.51 (2H, m), 1.50-1.59 (2H, m), 1.36-1.46 (4H, m), 1.33 (3H, d, J=6.6Hz), m/z=401.

Example 304: Synthesis of S-157

[0604] S-157 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrafluorothiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.1Hz, J=8.1Hz), 6.97-7.06 (1H, m), 6.86-6.89 (2H, m), 6.78-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.91 (2H, t, J=7.3Hz), 2.37-2.51 (2H, m), 1.51-1.58 (2H, m), 1.23-1.49 (6H, m), 1.34 (3H, d, J=6.6Hz), m/z=415.

Example 305: Synthesis of S-158

[0605] S-158 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrafluorothiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 6.97-7.05 (1H, m), 6.88-6.90 (2H, m), 6.78 (1H, m), 3.81 (3H, s), 3.74 (1H, q, J=6.7Hz), 2.91 (2H, t, J=7.3Hz), 2.38-2.51 (2H, m), 1.20-1.58 (8H, m), 1.36 (3H, d, J=6.7Hz), m/z=429.

Example 306: Synthesis of S-159

[0606] S-159 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrafluorothiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.22-7.26 (1H, m), 6.97-7.05 (1H, m), 6.89-6.92 (2H, m), 6.78-6.81 (1H, m), 3.81 (3H, s), 3.77 (1H, q, J=6.6Hz), 2.91 (2H, t, J=7.4Hz), 2.40-2.54 (2H, m), 1.17-1.57 (12H, m), 1.40 (3H, d, J=6.6Hz), m/z=443.

Example 307: Synthesis of S-160

[0607] S-160 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.84-7.89 (1H, m), 7.72 (1H, d, J=8.3Hz), 7.61 (1H, d, J=7.1Hz), 7.48 (1H, d, J=7.1Hz), 7.43-7.52 (3H, m), 6.95-7.03 (1H, m), 4.61 (1H, q, J=6.6Hz), 3.06 (2H, t, J=6.1Hz), 2.65-2.75 (2H, m), 1.48 (3H, d, J=6.6Hz), m/z=379.

Example 308: Synthesis of S-161

[0608] S-161 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.61 (1H, d, J=6.6Hz), 7.44-7.52 (3H, m), 6.95-7.04 (1H, m), 4.60 (1H, q, J=6.5Hz), 2.93-3.05 (2H, m), 2.61-2.75 (2H, m), 1.68-1.78 (2H, m), 1.48 (3H, d, J=6.5Hz), m/z=393.

Example 309: Synthesis of S-162

[0609] S-162 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.87 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.62 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 6.95-7.04 (1H, m), 4.61 (1H, q, J=6.6Hz), 2.90 (2H, t, J=6.7Hz), 2.48-2.62 (2H, m), 1.57-1.63 (4H, m), 1.48 (3H, d, J=6.6Hz), m/z=407.

Example 310: Synthesis of S-163

[0610] S-163 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.63 (1H, d, J=6.8Hz), 7.44-7.52 (3H, m), 6.95-7.04 (1H, m), 4.61 (1H, q, J=6.6Hz), 2.90 (2H, t, J=7.2Hz), 2.48-2.62 (2H, m), 1.38-1.58 (6H, m), 1.49 (3H, d, J=6.6Hz), m/z=421.

Example 311: Synthesis of S-164

[0611] S-164 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.1Hz), 7.65 (1H, d, J=7.1Hz), 7.45-7.53 (3H, m), 6.98-7.02 (1H, m), 4.63 (1H, q, J=6.6Hz), 2.89 (2H, t, J=7.3Hz), 2.47-2.62 (2H, m), 1.23-1.57 (8H, m), 1.50 (3H, d, J=6.6Hz), m/z=435.

Example 312: Synthesis of S-165

[0612] S-165 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.13 (1H, d, J=8.3Hz), 7.87-7.89 (1H, m), 7.78 (1H, d, J=8.0Hz), 7.47-7.56 (3H, m), 6.95-7.04 (1H, m), 4.79 (1H, q, J=6.4Hz), 2.87 (2H, t, J=7.3Hz), 2.52-2.68 (2H, m), 1.02-1.70 (10H, m), 1.65 (3H, d, J=6.4Hz), m/z=449.

Example 313: Synthesis of S-166

[0613] S-166 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.11 (1H, d, J=8.5Hz), 7.88-7.91 (1H, m), 7.80 (1H, d, J=8.3Hz), 7.44-7.57 (3H, m), 6.95-7.03 (1H, m), 4.89 (1H, bs), 2.88 (2H, t, J=7.3Hz), 2.54-2.72 (2H, m), 1.00-1.80 (15H, m), m/z=463.

Example 314: Synthesis of S-167

[0614] S-167 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiol by 5-chloro-2-mercaptobenzothiazole.

400MHz-^{1}H-NMR 7.80 (1H, d, J=1.7Hz), 7.63 (1H, dd, J=8.6Hz, J=1.2Hz), 7.18-7.28 (2H, m), 6.86-6.90 (2H, m), 6.74-6.78 (1H, m), 3.80 (3H, s), 3.77-3.82 (1H, m), 3.43-3.47 (2H, m), 2.85-3.00 (2H, m), 1.35 (3H, d, J=6.6Hz), m/z=378.

Example 315: Synthesis of S-168

[0615] S-168 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 5-chloro-2-mercaptobenzothiazole and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.79 (1H, d, J=2.0Hz), 7.63 (1H, d, J=8.2Hz), 7.19-7.27 (2H, m), 6.87-6.89 (2H, m), 6.77-6.79 (1H, m), 3.80 (3H, s), 3.74 (1H, q, J=6.6Hz), 3.33-3.47 (2H, m), 2.55-2.72 (2H, m), 1.93-2.00 (2H, m), 1.35 (3H, d, J=6.6Hz), m/z=392.

Example 316: Synthesis of S-169

[0616] S-169 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 5-chloro-2-mercaptobenzothiazole and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.82 (1H, d, J=2.0Hz), 7.63 (1H, d, J=8.5Hz), 7.21-7.27 (2H, m), 6.87-6.90 (2H, m), 6.76-6.79 (1H, m), 3.80 (3H, s), 3.73 (1H, q, J=6.6Hz), 3.32 (2H, t, J=7.3Hz), 2.45-2.60 (2H, m), 1.78-1.90 (2H, m), 1.59-1.65 (2H, m), 1.34 (3H, d, J=6.6Hz), m/z=406.

Example 317: Synthesis of S-170

[0617] S-170 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 5-chloro-2-mercaptobenzothiazole and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.83 (1H, d, J=2.0Hz), 7.63 (1H, d, J=7.6Hz), 7.20-7.27 (2H, m), 6.86-6.87 (2H, m), 6.75-6.78 (1H, m), 3.81 (3H, s), 3.72 (3H, s), 3.72 (1H, q, J=6.6Hz), 3.31 (2H, t, J=7.3Hz), 2.41-2.55 (2H, m), 1.80 (2H, tt, J=7.3Hz, J=7.3Hz), 1.43-1.57 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=420.

Example 318: Synthesis of S-171

[0618] S-171 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 5-chloro-2-mercaptobenzothiazole and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.82-7.83 (1H, m), 7.63 (1H, dd, J=8.6Hz, J=1.7Hz), 7.19-7.26 (2H, m), 6.88-6.93 (2H, m), 6.75-6.81 (1H, m), 3.82 (3H, s), 3.75-3.83 (1H, m), 3.30 (2H, t, J=7.3Hz), 2.42-2.56 (2H, m), 1.79 (2H, tt, J=7.3Hz, J=7.3Hz), 1.30-1.56 (6H, m), 1.40 (3H, d, J=6.4Hz), m/z=434.

Example 319: Synthesis of S-172

[0619] S-172 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 5-chloro-2-mercaptobenzothiazole and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.83 (1H, d, J=2.2Hz), 7.63 (1H, d, J=8.3Hz), 7.24-7.27 (2H, m), 6.89-6.92 (2H, m), 6.77-6.80 (1H, m), 3.81 (3H, s), 3.77 (1H, q, J=6.6Hz), 3.31 (2H, t, J=7.3Hz), 2.41-2.45 (2H, m), 1.79 (2H, tt, J=7.3Hz, =7.3Hz), 1.21-1.55 (8H, m), 1.40 (3H, d, J=6.6Hz), m/z=448.

Example 320: Synthesis of S-173

[0620] S-173 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 5-chloro-2-mercaptobenzothiazole and 1,8-dibromooctane.

400MHz-^{1}H-NMR 8.83 (1H, d, J=1.6Hz), 7.63 (1H, d, J=8.5Hz), 7.22-7.27 (2H, m), 6.91-6.94 (2H, m), 6.80 (1H, dd, J=8.3Hz, J=2.7Hz), 3.82 (3H, s), 3.78-3.85 (1H, m), 3.31 (2H, t, J=8.8Hz), 2.42-2.53 (2H, m), 1.79 (2H, tt, J=8.8Hz, J=8.8Hz), 1.20-1.57 (10H, m), 1.43 (3H, d, J=6.3Hz), m/z=462.

Example 321: Synthesis of S-174

[0621] S-174 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 398.

Example 322: Synthesis of S-175

[0622] S-175 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=7.3Hz), 7.84-7.88 (1H, m), 7.73-7.76 (2H, m), 7.64 (1H, d, J=7.8Hz), 7.62 (1H, d, J=8.3Hz), 7.43-7.48 (3H, m), 7.23-7.26 (1H, m), 4.63 (1H, q, J=6.6Hz), 3.35-3.50 (2H, m), 2.67-2.82 (2H, m), 2.01 (2H, tt, J=6.9Hz, J=6.9Hz), 1.50 (3H, d, J=6.6Hz), m/z=412.

Example 323: Synthesis of S-176

[0623] S-176 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.1Hz), 7.84-7.87 (1H, m), 8.80 (1H, d, J=1.9Hz), 7.73 (1H, d, J=8.3Hz), 7.65 (1H, d, J=6.8Hz), 7.62 (1H, d, J=8.3Hz), 7.43-7.52 (3H, m), 7.23-7.26 (1H, m), 4.63 (1H, q, J=6.6Hz), 3.31 (2H, t,

J=7.2Hz), 2.56-2.70 (2H, m), 1.82-1.90 (2H, m), 1.68 (2H, tt, J=7.2Hz, J=7.2Hz), 1.49 (3H, d, J=6.6Hz), m/z=426.

Example 324: Synthesis of S-177

[0624] S-177 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.82-7.87 (2H, m), 7.71-7.42 (1H, m), 7.58-7.64 (2H, m), 7.41-7.52 (3H, m), 7.23-7.26 (1H, m), 4.62 (1H, q, J=6.6Hz), 3.30 (2H, t, J=7.3Hz), 2.51-2.65 (2H, m), 1.79 (2H, tt, J=7.3Hz, J=7.3Hz), 1.58-1.60 (4H, m), 1.49 (3H, d, J=6.6Hz), m/z=440.

Example 325: Synthesis of S-178

[0625] S-178 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.5Hz), 7.82-7.88 (2H, m), 7.71-7.75 (1H, m), 7.65 (1H, d, J=7.1Hz), 7.62 (1H, d, J=8.5Hz), 7.42-7.52 (3H, m), 7.23-7.26 (1H, m), 4.63 (1H, q, J=6.6Hz), 3.29 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.78 (2H, tt, J=7.3Hz, J=7.3Hz), 1.32-1.56 (6H, m), 1.50 (3H, d, J=6.6Hz), m/z=454.

Example 326: Synthesis of S-179

[0626] S-179 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.86-7.88 (1H, m), 7.82-7.83 (1H, m), 7.72-7.78 (2H, m), 7.62 (1H, dd, J=8.6Hz, J=0.5Hz), 7.45-7.55 (3H, m), 7.23-7.26 (1H, m), 4.71 (1H, q, J=6.6Hz), 3.29 (1H, t, J=7.3Hz), 2.50-2.66 (2H, m), 1.71-1.80 (2H, m), 1.58 (3H, d, J=6.6Hz), 1.06-1.64 (8H, m), m/z=468.

Example 327: Synthesis of S-180

[0627] S-180 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.83 (1H, d, J=2.4Hz), 7.45 (1H, d, J=8.0Hz), 7.71 (1H.d.J=6.8Hz), 7.62 (1H, d, J=8.6Hz), 7.45-7.54 (1H, m), 7.23-7.24 (1H, m), 4.70 (1H, q, J=6.6Hz), 3.30 (2H, t, J=7.3Hz), 2.52-2.65 (2H, m), 1.68-1.84 (2H, m), 1.56 (3H, d, J=6.6Hz), 1.06-1.59 (10H, m), m/z=482.

Example 328: Synthesis of S-181

[0628] S-181 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiol by 2,3,5,6-tetrachloro-4-mercaptopyridine.

400MHz-^{1}H-NMR 7.23 (1H, d, J=8.0Hz), 6.84-6.87 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.69 (1H, q, J=6.6Hz), 3.06-3.19 (2H, m), 2.50-2.66 (2H, m), 1.69 (2H, tt, J=7.0Hz, J=7.0Hz), 1.33 (3H, d, J=6.6Hz), m/z=424, 426.

Example 329: Synthesis of S-182

[0629] S-182 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and 1,3-dibromopropane. m/z = 438, 440.

Example 330: Synthesis of S-183

[0630] S-183 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and 1,4-dibromobutane. m/z = 452, 454.

Example 331: Synthesis of S-184

[0631] S-184 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.88 (2H, m), 6.76-6.79 (1H, m), 3.05 (2H, t, J=7.3Hz), 3.81 (3H, s), 3.71 (1H, q, J=6.5Hz), 2.38-2.52 (2H, m), 1.55 (2H, tt, J=7.1Hz, J=7.1Hz), 1.36-1.50 (4H, m), 1.34 (3H, d, J=6.5Hz), m/z=466, 468.

Example 332: Synthesis of S-185

[0632] S-185 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 6.86-6.89 (2H, m), 6.76-6.81 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 3.05 (2H, t, J=7.3Hz), 2.37-2.52 (2H, m), 1.55 (2H, tt, J=7.2Hz, J=7.2Hz), 1.23-1.49 (6H, m), 1.34 (3H, d, J=6.6Hz), m/z=480, 482.

Example 333: Synthesis of S-186

[0633] S-186 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.24 (1H, dd, J=8.2Hz, J=8.2Hz), 6.87-6.90 (2H, m), 6.76-6.81 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 3.05 (2H, t, J=7.3Hz), 2.38-2.51 (2H, m), 1.55 (2H, tt, J=7.3Hz, J=7.3Hz), 1.20-1.49 (8H, m), 1.35 (3H, d, J=6.6Hz), m/z=494, 496.

Example 334: Synthesis of S-187

[0634] S-187 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 6.88-6.90 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.73 (1H, q, J=6.6Hz), 3.06 (2H, t, J=7.3Hz), 2.39-2.53 (2H, m), 1.55 (2H, tt, J=7.3Hz, J=7.3Hz), 1.20-1.50 (10H, m), 1.35 (3H, d, J=6.6Hz), m/z=508, 510.

Example 335: Synthesis of S-188

[0635] S-188 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 444, 446.

Example 336: Synthesis of S-189

[0636] S-189 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=7.8Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.60 (1H, d, J=6.8Hz), 7.44-7.52 (3H, m), 4.60 (1H, q, J=6.5Hz), 3.08-3.21 (2H, m), 2.61-2.75 (2H, m), 1.69-1.76 (2H, m), 1.49 (3H, d, J=6.5Hz), m/z=458, 460.

Example 337: Synthesis of S-190

[0637] S-190 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

40MHz-^{1}H-NMR 8.40 (1H, d, J=8.0Hz), 7.82-7.88 (1H, m), 7.69-7.75 (2H, m), 7.43-7.51 (3H, m), 4.04 (1H, q, J=6.6Hz), 2.47-2.70 (4H, m), 1.78-1.82 (4H, m), 1.53 (3H, d, J=6.6Hz), m/z=472, 474.

Example 338: Synthesis of S-191

[0638] S-191 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.75 (1H, d, J=8.0Hz), 7.66 (1H, d, J=6.8Hz), 7.45-7.53 (3H, m), 4.64 (1H, q, J=6.6Hz), 3.03 (2H, t, J=7.2Hz), 2.49-2.63 (2H, m), 1.35-1.60 (9H, m), m/z=486, 488.

Example 339: Synthesis of S-192

[0639] S-192 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.0Hz), 7.86-7.89 (1H, m), 7.76 (1H, d, J=8.3Hz), 7.70 (1H, bs), 7.46-7.54 (3H, m), 4.69 (1H, bs), 3.02 (2H, t, J=7.2Hz), 2.51-2.64 (2H, m), 1.25-1.60 (11H, m), m/z=500, 502.

Example 340: Synthesis of S-193

[0640] S-193 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.86-7.89 (1H, m), 7.70-7.78 (1H, m), 7.46-7.55 (3H, m), 4.74 (1H, bs), 3.03 (2H, t, J=7.2Hz), 2.50-2.66 (2H, m), 1.05-1.65 (13H, m), m/z=514, 516.

Example 341: Synthesis of S-194

[0641] S-194 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.86-7.89 (1H, m), 7.72-7.78 (2H, m), 7.46-7.54 (3H, m), 4.72 (1H, q, J=7.2Hz), 3.04 (2H, t, J=7.2Hz), 2.52-2.57 (2H, m), 1.00-1.56 (12H, m), 1.58 (3H, d, J=6.2Hz), m/z=528, 530.

Example 342: Synthesis of S-195

[0642] S-195 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 447.

Example 343: Synthesis of S-196

[0643] S-196 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing

the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.0Hz), 7.84-7.86 (1H, m), 7.73 (1H, d, J=8.0Hz), 7.60 (1H, d, J=6.8Hz), 7.43-7.51 (3H, m), 4.59 (1H, at J=6.2Hz), 3.02-3.15 (2H, m), 2.60-2.74 (2H, m), 1.67-1.77 (2H, m), 1.48 (3H, d, J=6.2Hz), m/z=461.

Example 344: Synthesis of S-197

[0644] S-197 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.2Hz), 7.85-7.88 (1H, m), 7.75 (1H, d, J=8.3Hz), 7.66 (1H, d, J=6.8Hz), 7.45-7.53 (3H, m), 4.64 (1H, q, J=6.4Hz), 2.99 (2H, t, J=7.3Hz), 2.50-2.63 (2H, m), 1.48-1.60 (4H, m), 1.52 (3H, d, J=6.4Hz), 1.26-1.42 (4H, m), m/z=503.

Example 345: Synthesis of S-198

[0645] S-198 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.66 (1H, d, J=6.8Hz), 7.45-7.52 (3H, m), 4.65 (1H, q, J=6.4Hz), 3.00 (2H, t, J=7.4Hz), 2.50-2.63 (2H, m), 1.47-1.60 (4H, m), 1.52 (3H, d, J=6.4Hz), 1.23-1.41 (6H, m), m/z=517.

Example 346: Synthesis of S-199

[0646] S-199 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 7.86-7.88 (1H, m), 7.75 (1H, d, J=8.3Hz), 7.69 (1H, d, J=6.1 Hz), 7.45-7.53 (3H, m), 4.67 (1H, q, J=6.4Hz), 3.01 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.20-1.70 (15H, m), m/z=531.

Example 347: Synthesis of S-200

[0647] S-200 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.51-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.64 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 4.62 (1H, q, J=6.6Hz), 3.02 (2H, t, J=7.4Hz), 2.50-2.62 (2H, m), 1.54-1.62 (2H, m), 1.49 (3H, d, J=6.6Hz), 1.00-1.54 (14H, m), m/z=559.

Example 348: Synthesis of S-201

[0648] S-201 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.66 (1H, d, J=7.1Hz), 7.45-7.53 (3H, m), 4.64 (1H, q, J=6.6Hz), 3.03 (2H, t, J=7.4Hz), 2.50-2.63 (2H, m), 1.20-1.63 (18H, m), 1.51 (3H, d, J=6.6Hz), m/z=587.

Example 349: Synthesis of S-202

[0649] S-202 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-isopropylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=7.8Hz), 7.84-7.87 (1H, m), 7.72 (1H, d, J=8.0Hz), 7.63 (1H, d, J=7.1 Hz), 7.41-7.54 (3H, m), 7.23-7.27 (2H, m), 7.13-7.16 (1H, m), 7.03-7.07 (1H, m), 4.63 (1H, q, J=6.5Hz), 3.45-3.54 (1H, m), 3.04 (2H, t, J=6.2Hz), 2.81 (2H, t, J=6.8Hz), 1.48 (2H, d, J=6.5Hz), 1.19-1.22 (6H, m), m/z=349.

Example 350: Synthesis of S-203

[0650] S-203 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-isopropylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=7.8Hz), 7.86 (1H, d, J=7.8Hz), 7.73 (1H, d, J=8.0Hz), 7.63 (1H, d, J=7.3Hz), 7.43-7.51 (3H, m), 7.22-7.29 (2H, m), 7.08-7.17 (2H, m), 4.60 (1H, q, J=6.4Hz), 3.42-3.50 (1H, m), 2.87-3.00 (2H, m), 2.62-2.76 (2H, m), 1.79-1.86 (2H, m), 1.48 (3H, d, J=6.4Hz), 1.18-1.22 (6H, m), m/z=363.

Example 351: Synthesis of S-204

[0651] S-204 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-isopropylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.87 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.63 (1H, d, J=6.8Hz), 7.44-7.51 (3H, m), 7.22-7.27 (2H, m), 7.07-7.18 (2H, m), 4.61 (1H, q, J=6.5Hz), 3.44-3.53 (1H, m), 2.85 (2H, t, J=6.8Hz), 2.51-2.65 (2H, m), 1.63-1.70 (4H, m), 1.48 (3H, d, J=6.5Hz), 1.21 (6H, d, J=6.8Hz), m/z=377.

Example 352: Synthesis of S-205

[0652] S-205 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-isopropylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.63 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 7.22-7.28 (2H, m), 7.08-7.18 (2H, m), 4.61 (1H, q, J=6.5Hz), 3.42-3.53 (1H, m), 2.85 (2H, t, J=7.3Hz), 2.49-2.62 (2H, m), 1.59-1.67 (2H, m), 1.40-1.56 (4H, m), 1.48 (3H, d, J=6.5Hz), 1.21 (6H, d, J=6.8Hz), m/z=391.

Example 353: Synthesis of S-206

[0653] S-206 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-isopropylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.64 (1H, d, J=6.8Hz), 7.41-7.52 (3H, m), 7.21-7.29 (2H, m), 7.09-7.17 (2H, m), 4.62 (1H, q, J=6.5Hz), 3.43-3.53 (1H, m), 2.84 (2H, t, J=7.3Hz), 2.49-2.62 (2H, m), 1.58-1.66 (2H, m), 1.45-1.55 (2H, m), 1.25-1.45 (4H, m), 1.49 (3H, m), 1.21-1.23 (6H, m), m/z=405.

Example 354: Synthesis of S-207

[0654] S-207 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-isopropylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.65 (1H, d, J=7.1Hz), 7.44-

7.52 (3H, m), 7.22-7.29 (2H, m), 7.09-7.17 (2H, m), 4.63 (1H, q, J=6.6Hz), 3.43-3.54 (1H, m), 2.85 (2H, t, J=7.4Hz), 2.49-2.62 (2H, m), 1.57-1.65 (2H, m), 1.36-1.55 (4H, m), 1.49 (3H, d, J=6.6Hz), 1.25-1.30 (4H, m), 1.20-1.25 (6H, m), m/z=419.

Example 355: Synthesis of S-208

[0655] S-208 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-isopropylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.5Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.65 (1H, d, J=7.1Hz), 7.44-7.53 (3H, m), 7.23-7.29 (2H, m), 7.09-7.17 (2H, m), 4.63 (1H, q, J=6.6Hz), 3.43-3.54 (1H, m), 2.85 (2H, t, J=7.4Hz), 2.50-2.62 (2H, m), 1.58-1.67 (2H, m), 1.24-1.52 (10H, m), 1.50 (3H, d, J=6.6Hz), 1.22 (6H, d, J=6.8Hz), m/z=433.

Example 356: Synthesis of S-209

[0656] S-209 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiol by 2,4,5-trichlorothiophenol.

400MHz-^{1}H-NMR 7.44 (1H, s), 7.29 (1H, s), 7.23 (1H, dd, J=8.3Hz, J=8.3Hz), 6.87-6.89 (2H, m), 6.76-6.79 (1H, m), 3.80 (3H, s), 3.76 (1H, q, J=6.6Hz), 3.03 (2H, t, J=6.5Hz), 2.70-2.85 (2H, m), 1.36 (3H, d, J=6.6Hz), m/z=389, 391.

Example 357: Synthesis of S-210

[0657] S-210 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4,5-trichlorothiophenol and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.44 (1H, s), 7.30 (1H, s), 7.22-7.25 (1H, m), 6.87-6.90 (2H, m), 6.77-6.80 (1H, m), 3.81 (3H, s), 3.74 (1H, q, J=6.5Hz), 2.89-3.03 (2H, m), 2.54-2.70 (2H, m), 1.77-1.85 (2H, m), 1.36 (3H, d, J=6.5Hz), m/z=403, 405.

Example 358: Synthesis of S-211

[0658] S-211 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4,5-trichlorothiophenol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.44 (1H, s), 7.21-7.27 (2H, m), 6.86-6.90 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.86-2.91 (2H, m), 2.43-2.58 (2H, m), 1.58-1.76 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=419, 421.

Example 359: Synthesis of S-212

[0659] S-212 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4,5-trichlorothiophenol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.44 (1H, s), 7.21-7.26 (2H, m), 6.87-6.90 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.89 (2H, t, J=7.3Hz), 2.41-2.55 (2H, m), 1.64-1.71 (2H, m), 1.43-1.56 (4H, m), 1.35 (3H, d, J=6.6Hz), m/z=431, 433.

Example 360: Synthesis of S-213

[0660] S-213 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4,5-trichlorothiophenol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.44 (1H, s), 7.21-7.26 (2H, m), 6.87-6.90 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 2.88 (2H, t, J=7.3Hz), 2.39-2.53 (2H, m), 1.63-1.71 (2H, m), 1.28-1.52 (6H, m), 1.34 (3H, d, J=6.6Hz), m/z=445, 447.

Example 361: Synthesis of S-214

[0661] S-214 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4,5-trichlorothiophenol and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.44 (1H, s), 7.21-7.26 (2H, m), 6.87-6.91 (2H, m), 6.76-6.80 (2H, m), 3.81 (3H, s), 3.73 (1H, q, J=6.6Hz), 2.89 (2H, t, J=7.3Hz), 2.39-2.53 (2H, m), 1.64-1.71 (2H, m), 1.39-1.48 (4H, m), 1.25-1.37 (6H, m), 1.35 (3H, d, J=6.6Hz), m/z=459, 461.

Example 362: Synthesis of S-215

[0662] S-215 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2,4,5-trichlorothiophenol and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.44 (1H, s), 7.25 (1H, s), 7.24 (1H, dd, J=8.0Hz, J=8.0Hz), 6.87-6.90 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.73 (1H, q, J=6.6Hz), 2.89 (1H, t, J=7.3Hz), 2.38-2.52 (2H, m), 1.64-1.71 (2H, m), 1.40-1.50 (4H, m), 1.35 (3H, d, J=6.6Hz), 1.25-1.35 (6H, m), m/z=473, 735.

Example 363: Synthesis of S-216

[0663] S-216 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.20 (1H, d, J=8.0Hz), 7.85-7.88 (1H, m), 7.75 (1H, d, J=8.0Hz), 7.64 (1H, d, J=7.1Hz), 7.45-7.52 (3H, m), 7.43 (1H, s), 7.29 (1H, s), 4.63 (1H, q, J=6.5Hz), 2.90-3.05 (2H, m), 2.64-2.80 (2H, m), 1.81-1.89 (2H, m), 1.52 (3H, d, J=6.5Hz), m/z=423, 425.

Example 364: Synthesis of S-217

[0664] S-217 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.86-7.88 (1H, m), 7.75 (1H, d, J=8.3Hz), 7.66 (1H, d, J=6.8Hz), 7.45-7.53 (3H, m), 7.44 (1H, s), 7.23 (1H, s), 4.65 (1H, q, J=6.6Hz), 2.86 (2H, t, J=7.3Hz), 2.51-2.66 (2H, m), 1.30-1.73 (8H, m), 1.52 (3H, d, J=6.6Hz), m/z=465, 467.

Example 365: Synthesis of S-218

[0665] S-218 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.86-7.88 (1H, m), 7.75 (1H, d, J=8.3Hz), 7.68 (1H, d, J=6.6Hz), 7.45-7.53 (3H, m), 7.43 (1H, s), 7.24 (1H, s), 4.66 (1H, q, J=6.4Hz), 2.87 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.25-1.70 (10H, m), 1.53 (3H, d, J=6.4Hz), m/z=423, 425.

Example 366: Synthesis of S-219

[0666] S-219 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by

2,4,5-trichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.86-7.89 (1H, m), 7.75 (1H, d, J=8.3Hz), 7.68 (1H, bs), 7.45-7.53 (3H, m), 7.44 (1H, s), 7.24 (1H, s), 4.67 (1H, bs), 2.88 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.23-1.71 (15H, m), m/z=493, 495.

Example 367: Synthesis of S-220

[0667] S-220 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 6-ethoxy-2-mercaptobenzothiazole and 1,3-dibromopropane. m/z = 402.

Example 368: Synthesis of S-221

[0668] S-221 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 6-ethoxy-2-mercaptobenzothiazole and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.71 (1H, d, J=8.8Hz), 7.20-7.24 (2H, m), 6.98 (1H, dd, J=9.0Hz, J=2.4Hz), 6.87-6.89 (2H, m), 6.77 (1H, ddd, J=8.0Hz, J=2.4Hz, J=1.0Hz), 4.06 (2H, q, J=6.9Hz), 3.80 (3H, s), 3.28 (2H, t, J=7.5Hz), 2.45-2.61 (2H, m), 1.75-1.88 (2H, m), 1.58-1.70 (2H, m), 1.44 (3H, t, J=7.5Hz), 1.35 (3H, d, J=6.9Hz), m/z=416.

Example 369: Synthesis of S-222

[0669] S-222 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 6-ethoxy-2-mercaptobenzothiazole and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.23 (1H, d, J=8.8Hz), 7.20-7.25 (2H, m), 6.99 (1H, dd, J=8.8Hz, J=2.4Hz), 6.87-6.90 (2H, m), 6.76-6.77 (1H, m), 4.03-4.11 (2H, m), 3.81 (3H, s), 3.72 (1H, q, J=6.6Hz), 3.27 (2H, t, J=7.6Hz), 2.41-2.54 (2H, m), 1.74-1.82 (2H, m), 1.41-1.56 (4H, m), 1.44 (3H, t, J=6.8Hz), 1.34 (3H, d, J=6.6Hz), m/z=430.

Example 370: Synthesis of S-223

[0670] S-223 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 6-ethoxy-2-mercaptobenzothiazole and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.73 (1H, d, J=9.0Hz), 7.20-7.25 (2H, m), 6.99 (1H, dd, J=8.8Hz, J=2.4Hz), 6.88-6.90 (2H, m), 6.77 (1H, ddd, J=8.3Hz, J=2.4Hz, J=1.0Hz), 4.06 (2H, q, J=7.0Hz), 3.81 (3H, s), 3.73 (1H, q, J=6.0Hz), 3.27 (2H, t, J=7.3Hz), 2.40-2.53 (2H, m), 1.74-1.81 (2H, m), 1.25-1.53 (6H, m), 1.44 (3H, t, J=7.0Hz), 1.35 (3H, d, J=6.0Hz), m/z=444.

Example 371: Synthesis of S-224

[0671] S-224 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 6-ethoxy-2-mercaptobenzothiazole and 1,7-dibromoheptane.

400MHz-^{1}H-NMR 7.72 (1H, d, J=9.0Hz), 7.25 (1H, dd, J=6.9Hz, J=6.9Hz), 7.21 (1H, d, J=2.4Hz), 6.98 (1H, dd, J=9.0Hz, J=2.4Hz), 6.78-6.82 (1H, m), 4.06 (3H, q, J=7.0Hz), 3.82 (3H, s), 3.79-3.85 (1H, m), 3.27 (2H, t, J=7.3Hz), 2.43-2.56 (2H, m), 1.73-1.80 (2H, m), 1.18-1.57 (1H, m), 1.44 (3H, t, J=7.0Hz), m/z=458.

Example 372: Synthesis of S-225

[0672] S-225 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 6-ethoxy-2-mercaptobenzothiazole and 1,8-dibromooctane.

400MHz-^{1}H-NMR 7.23 (1H, d, J=8.8Hz), 7.21-7.24 (2H, m), 6.99 (1H, dd, J=8.8Hz, J=2.7Hz), 6.87-6.91 (2H, m), 6.76-6.80 (1H, m), 4.06 (2H, q, J=7.0Hz), 3.81 (3H, s), 3.75 (1H, q, J=6.6Hz), 3.28 (2H, t, J=7.3Hz), 1.99-2.53 (2H, m), 1.74-1.81 (2H, m), 1.24-1.48 (10H, m), 1.44 (3H, t, J=7.0Hz), 1.37 (3H, d, J=6.6Hz), m/z=472.

Example 373: Synthesis of S-226

[0673] S-226 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 408.

Example 374: Synthesis of S-227

[0674] S-227 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 422.

Example 375: Synthesis of S-228

[0675] S-228 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.3Hz), 7.84-7.88 (1H, m), 7.73 (1H, d, J=8.3Hz), 7.70 (1H, d, J=9.0Hz), 7.65 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 7.20 (1H, d, J=2.4Hz), 6.97 (1H, dd, J=9.0Hz, J=2.4Hz), 4.63 (1H, q, J=6.6Hz), 4.05 (2H, q, J=7.0Hz), 3.28 (2H, dt, J=9.2Hz, J=1.2Hz), 2.55-2.69 (2H, m), 1.81-1.90 (2H, m), 1.63-1.72 (2H, m), 1.50 (3H, d, J=6.6Hz), 1.43 (3H, t, J=7.0Hz), m/z=436.

Example 376: Synthesis of S-229

[0676] S-229 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.83-7.88 (1H, m), 7.73 (1H, d, J=8.0Hz), 7.72 (1H, d, J=8.8Hz), 7.64 (1H, d, J=7.3Hz), 7.44-7.52 (3H, m), 7.20 (1H, d, J=2.4Hz), 6.98 (1H, dd, J=9.0Hz, J=2.7Hz), 4.62 (1H, q, J=6.5Hz), 4.06 (2H, q, J=7.0Hz), 3.27 (2H, t, J=7.3Hz), 2.52-2.65 (2H, m), 1.70-1.82 (2H, m), 1.49 (3H, d, J=6.5Hz), 1.44 (3H, t, J=7.0Hz), 1.41-1.60 (4H, m), m/z=450.

Example 377: Synthesis of S-230

[0677] S-230 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.5Hz), 7.82-7.88 (1H, m), 7.71-7.75 (2H, m), 7.66 (1H, d, J=7.0Hz), 7.41-7.53 (3H, m), 7.20 (1H, d, J=2.7Hz), 6.98 (1H, dd, J=8.8Hz, J=2.7Hz), 4.64 (1H, q, J=6.4Hz), 4.05 (2H, q, J=7.0Hz), 3.26 (2H, t, J=7.3Hz), 2.50-2.64 (2H, m), 1.73-1.81 (2H, m), 1.30-1.55 (6H, m), 1.51 (3H, d, J=6.4Hz), 1.43 (3H, t, J=7.0Hz), m/z=464.

Example 378: Synthesis of S-231

[0678] S-231 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.15 (1H, d, J=8.3Hz), 7.86-7.88 (1H, m), 7.72-7.78 (2H, m), 7.72 (1H, d, J=9.1Hz), 7.45-7.55 (3H, m), 6.98 (1H, dd, J=8.8Hz, J=2.4Hz), 4.72 (1H, q, J=6.4Hz), 4.05 (2H, q, J=7.0Hz), 3.25 (2H, t, J=7.3Hz), 2.52-2.66 (2H, m), 1.64-1.82 (2H, m), 1.59 (3H, d, J=6.4Hz), 1.43 (3H, t, J=7.0Hz), 1.03-1.68 (8H, m), m/z=478.

Example 379: Synthesis of S-232

[0679] S-232 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.5Hz), 7.86-7.88 (1H, m), 7.68-7.76 (3H, m), 7.45-7.53 (3H, m), 7.21 (1H, d, J=2.4Hz), 6.98 (1H, dd, J=8.8Hz, J=2.4Hz), 4.67 (1H, q, J=6.4Hz), 4.06 (2H, q, J=7.0Hz), 3.27 (2H, t, J=7.4Hz), 2.51-2.64 (2H, m), 1.69-1.80 (2H, m), 1.54 (3H, d, J=6.4Hz), 1.43 (3H, t, J=7.0Hz), 1.20-1.60 (10H, m), m/z=492.

Example 380: Synthesis of S-233

[0680] S-233 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dichlorothiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 375.

Example 381: Synthesis of S-234

[0681] S-234 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=7.6Hz), 7.84-7.89 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.63 (1H, d, J=7.1Hz), 7.45-7.56 (3H, m), 7.34-7.56 (1H, m), 7.33-7.34 (2H, m), 4.62 (1H, q, J=6.6Hz), 2.88-3.04 (2H, m), 2.63-2.78 (2H, m), 1.79-1.87 (2H, m), 1.50 (3H, d, J=6.6Hz), m/z=389.

Example 382: Synthesis of S-235

[0682] S-235 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.0Hz), 7.86-7.88 (1H, m), 7.75 (1H, bs), 7.67 (1H.bs), 7.45-7.53 (3H, m), 7.35-7.36 (1H, m), 7.13-7.14 (2H, m), 4.61-4.69 (1H, m), 2.84-2.89 (2H, m), 2.52-2.68 (2H, m), 1.48-1.73 (7H, m), m/z=403.

Example 383: Synthesis of S-236

[0683] S-236 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.0Hz), 7.86-7.88 (1H, m), 7.75 (1H, d, J=8.3Hz), 7.65 (1H, d, J=7.1Hz), 7.45-7.53 (3H, m), 7.35-7.37 (1H, m), 7.14-7.16 (2H, m), 4.64 (1H, q, J=6.4Hz), 2.87 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.60-1.68 (2H, m), 1.42-1.58 (4H, m), 1.51 (3H, d, J=6.4Hz), m/z=417.

Example 384: Synthesis of S-237

[0684] S-237 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.20 (1H, d, J=8.0Hz), 7.84-7.87 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.66 (1H, d, J=7.1Hz), 7.44-7.52 (3H, m), 7.19-7.25 (2H, m), 7.03 (1H, dd, J=8.5Hz, J=2.4Hz), 4.62 (1H, q, J=6.6Hz), 2.90-3.06 (2H, m), 2.62-2.80 (2H, m), 1.86 (2H, tt, J=7.0Hz, J=7.0Hz), 1.50 (3H, d, J=6.6Hz), m/z=389.

Example 385: Synthesis of S-238

[0685] S-238 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.73 (1H, d, J=8.0Hz), 7.64 (1H, d, J=6.8Hz), 7.44-7.53 (3H, m), 7.23-7.26 (1H, m), 7.14 (1H, d, J=2.4Hz), 7.03 (1H, dd, J=8.6Hz, J=2.4Hz), 4.63 (1H, q, J=6.5Hz), 2.87 (2H, t, J=7.3Hz), 2.51-2.64 (2H, m), 1.68 (1H, tt, J=7.3Hz, J=7.3Hz), 1.30-1.56 (6H, m), 1.50 (3H, d, J=6.5Hz), m/z=431.

Example 386: Synthesis of S-239

[0686] S-239 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 7.86-7.88 (1H, m), 7.75 (1H, d, J=8.0Hz), 7.70 (1H, d, J=7.1Hz), 7.45-7.53 (3H, m), 7.23 (1H, s), 7.14 (1H, d, J=2.4Hz), 7.03 (1H, d, J=2.4Hz, J=6.3Hz), 4.68 (1H, q, J=6.4Hz), 2.87 (2H, t, J=7.3Hz), 2.50-2.65 (2H, m), 1.66 (2H, tt, J=7.3Hz, 7.3Hz), 1.55 (3H, d, J=6.4Hz), 1.05-1.60 (8H, m), m/z=445.

Example 387: Synthesis of S-240

[0687] S-240 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 8.85-8.88 (2H, m), 7.75 (1H, d, J=8.3Hz), 7.70 (1H, d, J=7.1Hz), 7.45-7.54 (3H, m), 7.24 (1H, s), 7.14 (1H, d, J=2.4Hz), 7.02 (1H, dd, J=8.5Hz, J=2.4Hz), 4.69 (1H, q, J=6.5Hz), 2.86 (2H, t, J=6.8Hz), 2.51-2.65 (2H, m), 1.66 (2H, tt, J=6.8Hz, J=6.8Hz), 1.55 (3H, d, J=6.5Hz), 1.03-1.55 (10H, m), m/z=459.

Example 388: Synthesis of S-241

[0688] S-241 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-trifluoromethoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 391.

Example 389: Synthesis of S-242

[0689] S-242 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16-8.20 (1H, m), 7.82-7.89 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.62 (1H, d, J=6.6Hz), 7.44-7.52 (3H, m), 7.27-2.30 (2H, m), 7.08-7.11 (2H, m), 4.61 (1H, q, J=6.6Hz), 2.88-3.05 (2H, m), 2.61-2.76 (2H, m), 1.77-1.85 (2H, m), 1.49 (3H, d, J=6.6Hz), m/z=405.

Example 390: Synthesis of S-243

[0690] S-243 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.10 (1H, d, J=8.3Hz), 7.78-7.81 (1H, m), 7.66 (1H, d, J=8.3Hz), 7.57 (1H, d, J=6.8Hz), 7.37-7.45 (3H, m), 7.21-7.24 (2H, m), 7.03-7.05 (2H, m), 4.55 (1H, q, J=6.6Hz), 2.80 (2H, t, J=7.3Hz), 2.41-2.55 (2H, m), 1.49-1.57 (2H, m), 1.18-1.45 (8H, m), 1.42 (3H, d, J=6.6Hz), m/z=461.

Example 391: Synthesis of S-244

[0691] S-244 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.3Hz), 7.85-7.88 (1H, m), 7.74 (1H, d, J=8.0Hz), 7.65 (1H, d, J=7.1Hz), 7.44-7.53 (3H, m), 7.28-7.33 (2H, m), 7.10-7.13 (2H, m), 4.64 (1H, q, J=6.6Hz), 2.87 (2H, t, J=7.4Hz), 2.49-2.62 (2H, m), 1.56-1.65 (2H, m), 1.46-1.55 (2H, m), 1.50 (3H, d, J=6.6Hz), 1.33-1.42 (2H, m), 1.23-1.30 (6H, m), m/z=475.

Example 392: Synthesis of S-245

[0692] S-245 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 2-chlorobenzylmercaptan.

400MHz-^{1}H-NMR 7.33-7.38 (1H, m), 7.28-7.31 (1H, m), 7.47-7.26 (3H, m), 6.87-6.88 (2H, m), 6.78 (1H, ddd, J=8.1Hz, J=2.4Hz, J=1.0Hz), 3.81 (3H, s), 3.77 (2H, s), 3.70 (1H, q, J=6.5Hz), 2.57-2.73 (4H, m), 1.33 (3H, d, J=6.5Hz), m/z=335.

Example 393: Synthesis of S-246

[0693] S-246 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-chlorobenzylmercaptan and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.32-7.37 (2H, m), 7.14-7.25 (3H, m), 6.86-6.88 (2H, m), 6.77 (1H, ddd, J=8.3Hz, J=2.7Hz, J=1.0Hz), 3.80 (5H, s), 3.71 (1H, q, J=6.6Hz), 2.44-2.61 (4H, m), 1.70-1.78 (2H, m), 1.32 (3H, d, J=6.6Hz), m/z=349.

Example 394: Synthesis of S-247

[0694] S-247 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-chlorobenzylmercaptan and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.32-7.36 (2H, m), 7.14-7.27 (3H, m), 6.88-6.89 (2H, m), 6.76-6.79 (1H, m), 3.81 (3H, s), 3.80 (2H, s), 3.73 (1H, q, J=6.6Hz), 2.38-2.51 (4H, m), 1.30-1.60 (6H, m), 1.35 (3H, d, J=6.6Hz), m/z=377.

Example 395: Synthesis of S-248

[0695] S-248 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-chlorobenzylmercaptan and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.33-7.36 (2H, m), 7.14-7.27 (3H, m), 6.87-6.90 (2H, m), 6.74-6.79 (1H, m), 3.81 (5H, s), 3.72 (1H, q, J=6.6Hz), 2.37-2.51 (4H, m), 1.56 (2H, tt, J=7.3Hz, J=7.3Hz), 1.40-1.49 (2H, m), 1.20-1.38 (4H, m), 1.34 (3H, d, J=6.6Hz), m/z=391.

Example 396: Synthesis of S-249

[0696] S-249 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-chlorobenzylmercaptan and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.0Hz), 7.85-7.87 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.65 (1H, d, J=6.8Hz), 7.44-7.53 (3H, m), 7.24-7.34 (2H, m), 7.13-7.18 (2H, m), 4.60 (1H, q, J=6.6Hz), 3.77 (2H, s), 2.63-2.78 (4H, m), 1.48 (3H, d, J=6.6Hz), m/z=355.

Example 397: Synthesis of S-250

[0697] S-250 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.3Hz), 7.84-7.88 (1H, m), 7.74 (1H, d, J=8.3Hz), 7.63 (1H, d, J=6.8Hz), 7.44-7.52 (3H, m), 7.28-7.34 (2H, m), 7.12-7.18 (2H, m), 4.62 (1H, q, J=6.6Hz), 3.79 (2H, s), 2.45-2.72 (4H, m), 1.75-1.81 (2H, m), 1.49 (3H, d, J=6.6Hz), m/z=369.

Example 398: Synthesis of S-251

[0698] S-251 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol by 4-chlorobenzylmercaptan.

400MHz-^{1}H-NMR 7.21-7.26 (3H, m), 7.15-7.19 (2H, m), 6.85-6.87 (2H, m), 6.76-6.80 (1H, m), 3.81 (3H, s), 3.68 (1H, q, J=6.6Hz), 3.58 (2H, d, J=2.0Hz), 2.49-2.67 (4H, m), 1.33 (3H, d, J=6.6Hz), m/z=335.

Example 399: Synthesis of S-252

[0699] S-252 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 4-chlorobenzylmercaptan and 1,3-dibromopropane.

400MHz-^{1}H-NMR 7.19-7.27 (5H, m), 6.85-6.87 (2H, m), 6.76-6.79 (1H, m), 3.80 (3H, s), 3.69 (1H, q, J=6.6Hz), 3.63 (2H, s), 2.35-2.59 (4H, m), 1.63-1.73 (2H, m), 1.32 (3H, d, J=6.6Hz), m/z=349.

Example 400: Synthesis of S-253

[0700] S-253 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-chlorobenzylmercaptan and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 355.

Example 401: Synthesis of S-254

[0701] S-254 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=2.1Hz), 7.85-7.88 (1H, m), 7.73-7.75 (1H, d, J=8.1Hz), 7.62 (1H, d, J=7.4Hz), 7.45-7.53 (3H, m), 7.17-7.25 (4H, m), 4.60 (1H, q, J=6.6Hz), 3.61 (2H, s), 2.55-2.71 (2H, m), 2.37-2.48 (2H, m), 1.70-1.78 (2H, m), 1.48 (3H, d, J=6.6Hz), m/z=369.

Example 402: Synthesis of S-255

[0702] S-255 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-quinolinethiol and 1,4-dibromobutane.

400MHz-^{1}H-NMR 7.83-7.88 (2H, m), 7.69 (1H, d, J=8.0Hz), 7.59-7.63 (1H, m), 7.37-7.41 (1H, m), 7.15-7.24 (2H, m), 6.86-6.90 (2H, m), 6.73-6.78 (1H, m), 3.78 (3H, s), 3.73 (1H, q, J=6.8Hz), 3.30 (2H, t, J=6.8Hz), 2.47-2.61 (2H, m), 1.58-1.84 (4H, m), 1.33 (3H, d, J=6.8Hz), m/z=366.

Example 403: Synthesis of S-256

[0703] S-256 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-quinolinethiol and 1,5-dibromopentane.

400MHz-^{1}H-NMR 7.90 (1H, d, J=8.4Hz), 7.85 (1H, d, J=8.4Hz), 7.67-6.70 (1H, m), 7.60-7.64 (1H, m), 7.38-7.42

(1H, m), 7.22 (1H, dd, J=6.2Hz, J=6.2Hz), 7.18 (1H, d, J=8.4Hz), 6.86-6.90 (2H, m), 6.75-6.78 (1H, m), 3.80 (3H, s), 3.74 (1H, q, J=6.4Hz), 3.32 (2H, t, J=7.4Hz), 2.40-2.55 (2H, m), 1.76 (2H, tt, J=7.4Hz, J=7.4Hz), 1.44-1.59 (4H, m), 1.34 (3H, d, J=6.4Hz), m/z=380.

Example 404: Synthesis of S-257

[0704] S-257 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and 1-bromo-2-chloroethane respectively by 2-quinolinethiol and 1,6-dibromohexane.

400MHz-^{1}H-NMR 7.91 (1H, d, J=8.2Hz), 7.85 (1H, d, J=8.8Hz), 7.70 (1H, dd, J=8.0Hz, J=1.2Hz), 7.61-7.64 (1H, m), 7.38-7.43 (1H, m), 7.23 (1H, dd, J=8.0Hz, J=8.0Hz), 7.18 (1H, d, J=8.4Hz), 6.88-6.90 (2H, m), 6.76-6.79 (1H, m), 3.80 (3H, s), 3.74 (1H, q, J=6.4Hz), 3.34 (2H, t, J=7.2Hz), 2.41-2.54 (2H, m), 1.78 (2H, tt, J=7.2Hz, J=7.2Hz), 1.41-1.54 (4H, m), 1.35 (3H, d, J=6.4Hz), m/z=394.

Example 405: Synthesis of S-258

[0705] S-258 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-quinolinethiol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.18 (1H, d, J=8.0Hz), 7.83-7.87 (3H, m), 7.73 (1H, d, J=8.0Hz), 7.65-7.70 (2H, m), 7.56-7.60 (1H, m), 7.43-7.52 (3H, m), 7.37-7.42 (1H, m), 7.17 (1H, d, J=8.8Hz), 4.65 (1H, q, J=6.4Hz), 3.32 (2H, t, J=7.2Hz), 2.59-2.75 (2H, m), 1.67-1.87 (4H, m), 1.49 (3H, d, J=6.4Hz), m/z=386.

Example 406: Synthesis of S-259

[0706] S-259 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-quinolinethiol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=8.0Hz), 7.83-7.92 (3H, m), 7.58-7.74 (4H, m), 7.37-7.52 (4H, m), 7.18 (1H, d, J=8.4Hz), 4.63 (1H, q, J=6.4Hz), 3.32 (2H, t, J=7.4Hz), 2.54-2.66 (2H, m), 1.40-1.82 (6H, m), 1.49 (3H, d, J=6.4Hz), m/z=400.

Example 407: Synthesis of S-260

[0707] S-260 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 2-quinolinethiol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.17 (1H, d, J=8.4Hz), 7.37-7.82 (1H, m), 7.18 (1H, d, J=8.8Hz), 4.60-4.70 (1H, m), 3.30 (2H, t, J=7.4Hz), 2.46-2.83 (4H, m), 1.20-1.77 (9H, m), m/z=414.

Example 408: Synthesis of S-261

[0708] S-261 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.13-8.16 (1H, m), 7.83-7.89 (1H, m), 7.72 (1H, d, J=8.4Hz), 7.62 (1H, d, J=6.8Hz), 7.41-7.52 (3H, m), 7.21 (2H, d, J=8.0Hz), 7.02-7.05 (2H, m), 4.61 (1H, q, J=6.8Hz), 3.02 (2H, t, J=6.2Hz), 2.71-2.82 (2H, m), 2.29 (3H, s), 1.48 (3H, d, J=6.8Hz), m/z=321.

Example 409: Synthesis of S-262

[0709] S-262 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-methylthiopheol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

400MHz-^{1}H-NMR 8.16 (1H, d, J=7.6Hz), 7.83-7.88 (1H, m), 7.73 (1H, d, J=8.4Hz), 7.63 (1H, d, J=7.2Hz), 7.44-7.51 (3H, m), 7.21 (2H, d, J=8.0Hz), 7.04-7.07 (2H, m), 4.59 (1H, q, J=6.8Hz), 2.85-2.96 (2H, m), 2.61-2.74 (2H, m), 2.30 (3H, s), 1.79 (2H, tt, J=7.1Hz, J=7.1Hz), 1.47 (3H, d, J=6.8Hz), m/z=335.

Example 410: Synthesis of S-263

[0710] S-263 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 424.

Example 411: Synthesis of S-264

[0711] S-264 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 438.

Example 412: Synthesis of S-265

[0712] K-2117 (hydrochloride) (110 mg, 0.267 mmol) was dissolved in 2.2 ml of toluene (reagent grade). Next, m-chloroperbenzoic acid (56.0 mg, 0.325 mmol) was added thereto at room temperature and the obtained mixture was stirred at the same temperature for 1 hour.

[0713] After confirming the completion of the reaction by TLC, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium thiosulfate were added thereto at room temperature and the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate. The obtained organic layer was further concentrated under reduced pressure and the residue was purified by column chromatography [silica gel, 5 g, chloroform/methanol = 150/1] to thereby give a pale yellow, syrupy compound S-265 (82 mg, 0.214 mmol, yield: 78.3 %). m/z = 391.

Example 413: Synthesis of S-266

[0714] K-2117 (hydrochloride) (500 mg, 0.121 mmol) was dissolved in 20 ml of toluene (reagent grade). Next, m-chloroperbenzoic acid (58.0 mg, 0.336 mmol) was added thereto at room temperature and the obtained mixture was stirred at the same temperature for 8 hours. After confirming the completion of the reaction by TLC, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium thiosulfate were added thereto at room temperature and the reaction mixture was subjected to separatory extraction with chloroform and a saturated aqueous solution of sodium chloride and washed. The organic layer thus obtained was dried over anhydrous sodium sulfate. The obtained organic layer was further concentrated under reduced pressure and the residue was purified by column chromatography [silica gel, 5 g, chloroform/methanol = 150/1] to thereby give a pale yellow, syrupy compound S-266 (28 mg, 0.0686 mmol, yield: 56.7 %). m/z = 408.

Example 414: Synthesis of F-8

[0715] 2,5-Dichlorothiophenol (5 g) was dissolved in acetonitrile (100 ml). Then N-(2-bromoethylphthalimide) (7.8 g) was added thereto while stirring at 0 °C. Further, potassium carbonate (4.04 g) was added thereto. After 1 hour, water was added and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crystals thus obtained were washed with chloroform to thereby give N-(2-(2',5'-dichlorophenylthio)ethyl)phthalimide (F-8) (8.28 g). MS m/z: 351 (M^+).

Example 415: Synthesis of F-37

[0716] N-(2-(2',5'-Dichlorophenylthio)ethyl)phthalimide (F-8) (7.06 g) was added to ethanol (120 ml). After further adding hydrazine monohydrate (6.9 ml), the obtained mixture was heated under reflux for 1.5 hours. Then it was brought to room temperature and water was added thereto followed by extraction with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, chloroform/methanol = 20 : 1) to thereby give 2-(2',5'-dichlorophenylthio)ethylamine (F-37) (4.29 g). MS m/z : 221 (M^+).

Example 416: Synthesis of F-12

[0717] 2-(2',5'-Dichlorophenylthio)ethylamine (F-37) (250 mg) was mixed with 3'-methoxyacetophenone (0.15 ml). After adding titanium tetraisopropoxide (0.4 ml), the mixture was stirred for 3 hours. After adding ethanol (3 ml), sodium boron hydride (43 mg) was further added to the reaction mixture under ice-cooling. Then the mixture was brought to room temperature and stirred for 15 hours. The reaction mixture was concentrated and ethyl acetate and water were added thereto. The insoluble matters were filtered off and the organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, chloroform/methanol = 50 : 1) to thereby give (±)-N-(1-(3-methoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-12) (146 mg). MS m/z : 355 (M^+).

Example 417: Synthesis of F-13

[0718] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimehtoxyacetophenone to thereby give (±)-N-(1-(3,4-dimethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z : 385 (M^+).

Example 418: Synthesis of F-14

[0719] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-methylacetophenone to thereby give (±)-N-(1-(3-methylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-14). MS m/z : 339 (M^+).

Example 419: Synthesis of F-15

[0720] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-methylacetophenone to thereby give (±)-N-(1-(4-methylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 339 (M^+).

Example 420: Synthesis of F-16

[0721] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4',5'-trimethoxyacetophenone to thereby give (±)-N-(1-(3,4,5-trimethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-16). MS m/z: 415 (M^+).

Example 421: Synthesis of F-17

[0722] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxyacetophenone to thereby give (±)-N-(1-(4-hydroxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-17). MS m/z: 341 (M^+).

Example 422: Synthesis of F-18

[0723] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethyl)acetophenone to thereby give (±)-N-(1-(3-trifluoromethylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-18). MS m/z: 393 (M^+).

Example 423: Synthesis of F-21

[0724] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxy-3'-methoxyacetophenone to thereby give (±)-N-(1-(4-hydroxy-3-methoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-21). MS m/z : 371 (M^+).

Example 424: Synthesis of F-22

[0725] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-bromoacetophenone to thereby give (±)-N-(1-(4-bromophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-22). MS m/z : 405 (M^+).

Example 425: Synthesis of F-23

[0726] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-bromoacetophenone to thereby give (±)-N-(1-(3-bromophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-23). MS m/z : 405 (M^+).

Example 426: Synthesis of F-24

[0727] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-bromoacetophenone to thereby give (±)-N-(1-(2-bromophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-24). MS m/z : 405 (M^+).

Example 427: Synthesis of F-29

[0728] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dihydroxyacetophenone to thereby give (±)-N-(1-(3,4-dihydroxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-29). MS m/z : 357 (M^+).

Example 428: Synthesis of F-30

[0729] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dichloroacetophenone to thereby give (±)-N-(1-(2,5-chlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-30). MS m/z : 395 (M^+).

Example 429: Synthesis of F-31

[0730] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoro-4'-methoxyacetophenone to thereby give (±)-N-(1-(3-fluoro-4-methoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-31). MS m/z: 373 (M^+).

Example 430: Synthesis of F-35

[0731] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethoxy)acetophenone to thereby give (±)-N-(1-(3-trifluoromethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-35). MS m/z: 409 (M^+).

Example 431: Synthesis of F-48

[0732] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethylacetophenone to thereby give (±)-N-(1-(3,4-dimethylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-48). MS m/z: 353 (M^+).

Example 432: Synthesis of F-49

[0733] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-chloroacetophenone to thereby give (±)-N-(1-(2-chlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-49). MS m/z: 359 (M^+).

Example 433: Synthesis of F-50

[0734] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-chloroacetophenone to thereby give (±)-N-(1-(3-chlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-50). MS m/z: 359 (M^+).

Example 434: Synthesis of F-51

[0735] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-chloroacetophenone to thereby give (±)-N-(1-(4-chlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-51).

MS m/z : 359 (M^+).

Example 435: Synthesis of F-52

[0736] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoroacetophenone to thereby give (±)-N-(1-(3-fluorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-52). MS m/z: 343 (M^+).

Example 436: Synthesis of F-53

[0737] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-fluoroacetophenone to thereby give (±)-N-(1-(4-fluorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-53). MS m/z: 343 (M^+).

Example 437: Synthesis of F-54

[0738] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dimethylacetophenone to thereby give (±)-N-(1-(2,5-dimethylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-54). MS m/z : 353 (M^+).

Example 438: Synthesis of F-55

[0739] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dimethylacetophenone to thereby give (±)-N-(1-(2,4-dimethylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-55). MS m/z: 353 (M^+).

Example 439: Synthesis of F-57

[0740] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dichloroacetophenone to thereby give (±)-N-(1-(2,4-dichlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-57). MS m/z: 395 (M^+).

Example 440: Synthesis of F-58

[0741] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dichloroacetophenone to thereby give (±)-N-(1-(3,4-dichlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-58). MS m/z: 395 (M^+).

Example 441: Synthesis of F-63

[0742] 3'-Hydroxyacetophenone (200 mg) was dissolved in acetonitrile (4 ml). After adding ethyl iodide (0.2 ml) and potassium carbonate (347 mg), the mixture was stirred at 70 °C for 9 hours. After 9 hours, water and ethyl acetate were added to the reaction mixture followed by separation. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane : ethyl acetate = 8 : 1) to thereby give 204 mg of 3'-ethoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-ethoxyacetophenone to thereby give (±)-N-(1-(3-ethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-63). MS m/z: 369 (M^+).

Example 442: Synthesis of F-64

[0743] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by n-propyl iodide to thereby give 3'-n-propoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-propoxyacetophenone to thereby give (±)-N-(1-(3-n-propoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-64). MS m/z: 383 (M^+).

Example 443: Synthesis of F-65

[0744] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by n-butyl iodide to thereby give 3'-n-butoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-butoxyacetophenone to thereby give (±)-N-(1-(3-n-butoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-65). MS m/z: 397 (M^+).

Example 444: Synthesis of K-2255

[0745] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by n-hexyl bromide to thereby give 3'-n-hexyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-hexyloxyacetophenone to thereby give (±)-N-(1-(3-n-hexyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2255). MS m/z: 425 (M^+).

Example 445: Synthesis of F-67

[0746] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by isopropyl iodide to thereby give 3'-isopropoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isopropoxyacetophenone to thereby give (±)-N-(1-(3-isopropoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-67). MS m/z : 383 (M^+).

Example 446: Synthesis of F-68

[0747] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by dodecane iodide to thereby give 3'-dodecylxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-dodecyloxyacetophenone to thereby give (±)-N-(1-(3-n-dodecyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-68). MS m/z : 509 (M^+).

Example 447: Synthesis of F-69

[0748] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by isobutyl iodide to thereby give 3'-isobutoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isobutoxyacetophenone to thereby give (±)-N-(1-(3-isobutoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-69). MS m/z: 397 (M^+).

Example 448: Synthesis of K-2258

[0749] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 4-chrolobenzyl bromide to thereby give 3'-(4-chlorobenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-chlorobenzyloxy)acetophenone to thereby give (±)-N-(1-(3-(4-chlorobenzyloxy)phenyl)ethyl)-2(2',5'-dichlorophenylthio)ethylamine (K-2258). MS m/z: 465 (M^+).

Example 449: Synthesis of F-71

[0750] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 2-chlorobenzyl bromide to thereby give 3'-(2-chlorobenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chlorobenzyloxy)acetophenone to thereby give (±)-N-(1-(3-(2-chlorobenzyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-71). MS m/z: 465 (M^+).

Example 450: Synthesis of F-72

[0751] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by benzyl bromide to thereby give 3'-benzyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-benzyloxyacetophenone to thereby give (±)-N-(1-(3-benzyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-72). MS m/z: 431 (M^+).

Example 451: Synthesis of F-73

[0752] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 2,6-dichlorobenzyl bromide to thereby give 3'-(2,6-dichlorobenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2,6-dichlorobenzyloxy)acetophenone to thereby give (±)-N-(1-(3-(2,6-dichlorobenzyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-73). MS m/z: 501 (M^+).

Example 452: Synthesis of K-2260

[0753] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 1-bromo-6-chlorohexane to thereby give 3'-(6-chlorohexyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(6-chlorohexyloxy)acetophenone to thereby give (±)-N-(1-(3-(6-chlorohexyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2260). MS m/z : 459 (M^+).

Example 453: Synthesis of F-75

[0754] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 1-bromo-6-chlorohexane to thereby give 3'-(2-chloroethoxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chloroethoxy)acetophenone to thereby give (±)-N-(1-(3-(2-chloroethoxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-75). MS m/z : 403 (M^+).

Example 454: Synthesis of F-76

[0755] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 2-methylbenzyl bromide to thereby give 3'-(2-methylbenzyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-methylbenzyl)acetophenone to thereby give (±)-N-(1-(3-(2-methylbenzyl)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-76). MS m/z: 445 (M^+).

Example 455: Synthesis of K-2268

[0756] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 4-methylbenzyl bromide to thereby give 3'-(4-methylbenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-methylbenzyloxy)acetophenone to thereby give (±)-N-(1-(3-(4-methylbenzyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2268). MS m/z : 445 (M^+).

Example 456: Synthesis of F-78

[0757] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylfuran to thereby give (±)-N-(1-(2-(5-methyl)furanyl)ethyl)-2-(2',5'dichlorophenylthio)ethylamine (F-78). MS m/z: 329 (M^+).

Example 457: Synthesis of F-79

[0758] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylfuran to thereby give (±)-N-(1-(2-furanyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-79). MS m/z : 315 (M^+).

Example 458: Synthesis of F-80

[0759] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-1-methylpyrrole to thereby give (±)-N-(1-(2-(1-methyl)pyrrolyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-80). MS m/z : 328 (M^+).

Example 459: Synthesis of F-81

[0760] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylthiophene to thereby give (±)-N-(1-(2-thienyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-81). MS m/z : 331 (M^+).

Example 460: Synthesis of F-82

[0761] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2,5-dimethylfuran to thereby give (±)-N-(1-(3-(2,5-dimethyl)furanyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-82). MS m/z: 343 (M^+).

Example 461: Synthesis of F-83

[0762] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylthiophene to thereby give (±)-N-(1-(3-thienyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-83). MS m/z : 331 (M^+).

Example 462: Synthesis of F-84

[0763] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylthiophene to thereby give (±)-N-(1-(2-(5-methyl)thienyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-84). MS m/z: 345 (M^+).

Example 463: Synthesis of F-85

[0764] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-1-methylpyrrole to thereby give (±)-N-(1-(3-(1-methyl)pyrrolyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-85). MS m/z : 329 (M^+).

Example 464: Synthesis of F-86

[0765] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 5-acetyl-2,4-dimethylthiazle to thereby give (±)-N-(1-(5-(2,4-dimethyl)thiazolyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-86). MS m/z : 360 (M^+).

Example 465: Synthesis of F-90

[0766] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by cyclohexylmethyl bromide to thereby give 3'-(cyclohexylmethoxybenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(cyclohexylmethoxybenzyloxy)-acetophenone to thereby give (±)-N-(1-(3-(cyclohexylmethoxybenzyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-90). MS m/z : 437 (M^+).

Example 466: Synthesis of F-91

[0767] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyridine to thereby give (±)-N-(1-(2-pyridyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-91). MS m/z : 327 (M^+).

Example 467: Synthesis of F-92

[0768] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylpyridine to thereby give (±)-N-(1-(3-pyridyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-92). MS m/z : 326 (M^+).

Example 468: Synthesis of F-93

[0769] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4-acetylpyridine to thereby give (±)-N-(1-(4-pyridyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-93). MS m/z : 326 (M^+).

Example 469: Synthesis of F-94

[0770] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyrazine to thereby give (±)-N-(1-(2-pyrazyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-94). MS m/z : 327 (M^+).

Example 470: Synthesis of F-95

[0771] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2-(methylaminesulfonyl)thiophene to thereby give (±)-N-(1-(3-(2-methylaminosulfonyl)thienyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-95). MS m/z : 425 (M^+).

Example 471: Synthesis of F-96

[0772] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylindole to thereby give (±)-N-(1-(3-indolyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-96). MS m/z : 364 (M^+).

Example 472: Synthesis of F-97

[0773] Di(4-trifluoromethyl)benzylamine (450 mg) was dissolved in methylene chloride (10 ml) and bromoacetic acid (186 mg) was added thereto. After further adding WSC. HCl (390 mg), the reaction mixture was heated under reflux for 30 minutes. Then it was brought back to room temperature and separated into aqueous and ethyl acetate layers. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane : ethyl acetate = 3 : 1) to thereby give 510 mg of a bromo compound. This bromo compound (500 mg) was dissolved in acetonitrile (10 ml) and potassium carbonate (763 mg) and (R)-(+)-1-(1-naphthyl)ethylamine (0.18 ml) was added thereto. After further adding tetrabutylammonium iodide (41 mg), the mixture was heated under reflux. After 2 hours, it was brought back to room temperature and separated into aqueous and chloroform layers. The organic layer washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane : ethyl acetate = 2 : 1) to thereby give 280 mg of a F-97. MS m/z : 544 ($M+1^+$).

Example 473: Synthesis of F-98

[0774] The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethyl)benzylamine by (4-trifluoromethoxy)benzylamine to thereby give F-98. MS m/z: 576 ($M+1^+$).

Example 474: Synthesis of F-99

[0775] The procedure employed for the synthesis of F-97 was repeated but replacing the bromoacetic acid by 5-bromopentanoic acid to thereby give F-99. MS m/z : 586 (M^+).

Example 475: Synthesis of F-100

[0776] The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethyl)benzylamine by (4-chloro)benzylamine to thereby give F-100. MS m/z: 476 (M^+).

Example 476: Synthesis of F-101

[0777] The procedure employed for the synthesis of F-99 was repeated but replacing the di(4-trifluoromethyl)benzylamine by di(4-trifluoromethoxy)benzylamine to thereby give F-101. MS m/z: 618 (M^+).

Example 477: Synthesis of F-102

[0778] The procedure employed for the synthesis of F-98 was repeated but replacing the bromoacetic acid by 4-bromobutyric acid to thereby give F-102. MS m/z : 604 (M^+).

Example 478: Synthesis of F-103

[0779] The procedure employed for the synthesis of F-98 was repeated but replacing the bromoacetic acid by 6-bromohexanoic acid to thereby give F-103. MS m/z : 632 (M^+).

Example 479: Synthesis of F-104

[0780] The procedure employed for the synthesis of F-103 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by di(4-trifluoromethyl)benzylamine to thereby give F-104. MS m/z : 600 (M^+).

Example 480: Synthesis of F-105

[0781] The procedure employed for the synthesis of F-101 was repeated but replacing the di(4-trifluoromethyl)benzylamine by di(4-chloro)benzylamine to thereby give F-105. MS m/z: 533 ($M+1^+$).

Example 481: Synthesis of F-106

[0782] The procedure employed for the synthesis of F-102 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by di(4-chloro)benzylamine to thereby give F-106. MS m/z : 505 ($M+1^+$).

Example 482: Synthesis of F-107

[0783] The procedure employed for the synthesis of F-99 was repeated but replacing the di(4-trifluoromethyl)benzylamine by di(4-chloro)benzylamine to thereby give F-107. MS m/z : 519 ($M+1^+$).

Example 483: Synthesis of F-108

[0784] The procedure employed for the synthesis of F-98 was repeated but replacing the bromoacetic acid by 8-bromooctanoic acid to thereby give F-108. MS m/z : 660 (M^+).

Example 484: Synthesis of F-109

[0785] The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by di(4-trifluoromethyl)benzylamine to thereby give F-109. MS m/z : 628 (M^+).

Example 485: Synthesis of F-110

[0786] The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethyl)benzylamine by di(4-chloro)benzylamine to thereby give F-110. MS m/z : 561 ($M+1^+$).

Example 486: Synthesis of F-111

[0787] The procedure employed for the synthesis of F-99 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-111. MS m/z: 587 ($M+1^+$).

Example 487: Synthesis of F-112

[0788] The procedure employed for the synthesis of F-103 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-112. MS m/z : 601 ($M+1^+$).

Example 488: Synthesis of F-113

[0789] The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethyl)ben-

zylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-113. MS m/z : 544 (M^+).

Example 489: Synthesis of F-114

[0790] The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-114. MS m/z : 628 (M^+).

Example 490: Synthesis of F-115

[0791] The procedure employed for the synthesis of F-102 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-115. MS m/z : 572 (M^+).

Example 491: Synthesis of F-116

[0792] The procedure employed for the synthesis of F-115 was repeated but replacing the 4-bromobutyric acid by 12-bromododecanoic acid to thereby give F-116. MS m/z : 684 (M^+).

Example 492: Synthesis of F-117

[0793] The procedure employed for the synthesis of F-102 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by dibenzylamine to thereby give F-117. MS m/z : 450 (M^+).

Example 493: Synthesis of F-118

[0794] The procedure employed for the synthesis of F-103 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by dibenzylamine to thereby give F-118. MS m/z : 464 (M^+).

Example 494: Synthesis of F-119

[0795] The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by dibenzylamine to thereby give F-119. MS m/z : 492 (M^+).

Example 495: Synthesis of F-120

[0796] The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by dibenzylamine to thereby give F-120. MS m/z : 408 (M^+).

Example 496: Synthesis of S-267

[0797] S-267 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-tert-butylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 363.

Example 497: Synthesis of S-268

[0798] S-268 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 377.

Example 498: Synthesis of S-269

[0799] S-269 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 391.

Example 499: Synthesis of S-270

[0800] S-270 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing

the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 405.

Example 500: Synthesis of S-271

[0801] S-271 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 419.

Example 501: Synthesis of S-272

[0802] S-272 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 433.

Example 502: Synthesis of S-273

[0803] S-273 was synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-α-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z = 447.

Example 503: Synthesis of S-274

[0804] S-274 was synthesized by almost the same method as the one employed for the synthesis of S-265 but replacing the K-2117 by K-2027. m/z = 399.

Example 504: Synthesis of S-275

[0805] S-275 was synthesized by almost the same method as the one employed for the synthesis of S-265 but replacing the K-2117 by K-2076. m/z = 433.

Example 505: Synthesis of S-276

[0806] S-276 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-(trifluoromethoxy)benzaldehyde by 4-dimethylaminobenzaldehyde.

Example 506: Synthesis of S-277

[0807] S-277 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-tert-butylbenzylamine and 3,4-dichlorobenzaldehyde.

Example 507: Synthesis of S-278

[0808] S-278 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-nitrobenzylamine and 3,4-dichlorobenzaldehyde.

Example 508: Synthesis of S-279

[0809] S-279 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 3,4-dichlorobenzylamine and 4-dimethylaminobenzaldehyde.

Example 509: Synthesis of S-280

[0810] S-280 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-(trifluoromethoxy)benzaldehyde by 3,4-dimethoxybenzaldehyde.

Example 510: Synthesis of S-281

[0811] S-281 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-(trifluoromethyl)benzylamine and 3,4-dimethoxybenzaldehyde.

Example 511: Synthesis of S-282

[0812] S-282 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-(trifluoromethoxy)benzaldehyde by 3,4-dimethylbenzaldehyde.

Example 512: Synthesis of S-283

[0813] S-283 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-(trifluoromethyl)benzylamine and 3,4-dimethylbenzaldehyde.

Example 513: Synthesis of S-284

[0814] S-284 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-(trifluoromethoxy)benzaldehyde by 3,4-methylenedioxybenzaldehyde.

Example 514: Synthesis of S-285

[0815] S-285 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-tert-butylbenzylamine and 4-tert-butylbenzaldehyde.

Example 515: Synthesis of S-286

[0816] S-286 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-(trifluoromethoxy)benzaldehyde by 4-chlorobenzaldehyde.

Example 516: Synthesis of S-287

[0817] S-287 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-chlorobenzylamine and 4-pyridinecarboxyaldehyde.

Example 517: Synthesis of S-288

[0818] S-288 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-(trifluoromethyl)benzylamine and 4-pyridinecarboxyaldehyde.

Example 518: Synthesis of S-289

[0819] S-289 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 3,4-dichlorobenzylamine and 4-phenylbenzaldehyde.

Example 519: Synthesis of S-290

[0820] S-290 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 3,4-dimethylbenzylamine and 4-phenylbenzaldehyde.

Example 520: Synthesis of S-291

[0821] S-291 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 3,4-dimethoxybenzylamine and 4-phenylbenzaldehyde.

Example 521: Synthesis of S-292

[0822] S-292 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 3,4-dichlorobenzylamine and 4-methylthiobenzaldehyde.

Example 522: Synthesis of S-293

[0823] S-293 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 3,4-dimethylbenzylamine and 4-methylthiobenzaldehyde.

Example 523: Synthesis of S-294

[0824] S-294 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 3,4-dimethoxybenzylamine and 4-methylthiobenzaldehyde.

Example 524: Synthesis of S-295

[0825] S-295 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-(trifluoromethyl)benzylamine and 3-chloro-4-fluorobenzaldehyde.

Example 525: Synthesis of S-296

[0826] S-296 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-(trifluoromethoxy)benzaldehyde by 3-chloro-4-fluorobenzaldehyde.

Example 526: Synthesis of S-297

[0827] S-297 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-(trifluoromethyl)benzylamine and 4-chloro-3-nitrobenzaldehyde.

Example 527: Synthesis of S-298

[0828] S-298 can be synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-(trifluoromethoxy)benzaldehyde by 4-chloro-3-nitrobenzaldehyde.

Example 528: Synthesis of S-299

[0829] S-299 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-chlorobenzylamine and 5-methyl-2-thiophenecarboxyaldehyde.

Example 529: Synthesis of S-300

[0830] S-300 was synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methylbenzylamine and 4-(trifluoromethoxy)benzaldehyde respectively by 4-(trifluoromethyl)benzylamine and 5-methyl-2-thiophenecarboxyaldehyde.

Example 530:

[0831] The activities of the compounds of the present invention on calcium receptors were measured. The measurement was performed in accordance with the method described in Example 4 of Nemeth et al., PCT/US95/13704 (International Publication No. WO96/12697). In brief, HEK293 cells were transfected with a plasmid pHuPCaR4.0 containing a human calcium receptor gene and loaded with fluo-3. The loading was carried out by incubating the cells at 37 °C for 1 hour in Dulbecco's modified Eagle's medium which contained about 5 μM of fluo-3/AM and had been buffered with 20 mM HEPES. Next, the cells were rinsed with Hank's balanced salt solution which contained 1 mM $CaCl_2$ and 1 mM $MgCl_2$ and had been buffered with 20 mM HEPES. Then each test compound was added to the cells and the fluorescence was measured with the use of an excitation wavelength of 485 nm and an emission wavelength of 540 nm. The results are shown in Table 1.

Table 1

Compound	EC_{50}(μM)	Compound	EC_{50}(μM)
2	13	46	0.93
6	7.6	52	0.48
8	1.9	53	1.6
10	1.0	56	0.28
12	1.2	59	1.02
14	2.9	62	0.509
16	0.55	65	0.524
18	0.75	68	0.65
20	3.2	71	0.27
22	0.31	74	7.2
24	0.44	77	1.0
26	1.8	80	0.464
28	1.6	83	1.0
30	0.071	88	3.2
32	0.051	93	0.11
34	0.71	103	0.3
36	0.21	106	0.064
38	0.98	109	0.27
40	5.1	112	0.078
42	0.14	117	0.2
44	0.15	123	0.1

Table 1 (cont.)

Compound	$EC_{50}(\mu M)$	Compound	$EC_{50}(\mu M)$
K-2003	0.29	K-2048	0.73
K-2004	0.42	K-2049	0.83
K-2005	0.43	K-2050	0.55
K-2006	0.77	K-2051	0.34
K-2007	0.47	K-2052	5.7
K-2008	0.86	K-2055	0.057
K-2010	0.14	K-2056	0.039
K-2011	0.21	K-2057	0.41
K-2012	0.87	K-2058	0.39
K-2015	0.49	K-2059	0.27
K-2016	0.36	K-2061	0.15
K-2017	0.36	K-2066	0.26
K-2018	0.33	K-2075	0.14
K-2027	0.39	K-2076	6.2
K-2030	0.049	K-2078	0.17
K-2033	0.35	K-2079	0.2
K-2034	0.061	K-2080	0.77
K-2035	0.22	K-2082	2.81
K-2040	0.08	K-2084	0.12
K-2041	0.1	K-2085	0.13
K-2045	0.87	K-2087	0.087
K-2046	0.14	K-2117	0.043
K-2047	0.13	K-2177	0.075

Table 1 (cont.)

Compound	$EC_{50}(\mu M)$	Compound	$EC_{50}(\mu M)$
K-2240	0.36	K-2267	0.014
K-2243	0.092	K-2268	0.089
K-2246	0.12	K-2269	0.071
K-2247	0.13	K-2270	0.14
K-2248	0.078	K-2271	0.14
K-2249	0.082	K-2272	0.052
K-2250	0.076	K-2273	0.16
K-2251	0.051	K-2274	1.2
K-2252	0.018	K-2275	0.27
K-2253	0.19	K-2276	0.064
K-2254	0.088	K-2277	0.93
K-2255	9.6	K-2278	2.50
K-2256	0.18	K-2279	0.63
K-2257	0.039	K-2280	0.27
K-2258	0.38	K-2281	0.43
K-2259	0.0024	K-2282	0.34
K-2260	0.096	K-2283	0.093
K-2261	0.026	K-2284	0.36
K-2262	0.084	K-2285	0.32
K-2263	0.11	K-2286	0.62
K-2264	0.016	K-2287	0.062
K-2265	0.061	K-2288	0.14
K-2266	0.036	K-2289	0.074

Table 1 (cont.)

Compound	$EC_{50}(\mu M)$	Compound	$EC_{50}(\mu M)$
K-2290	0.1	K-2306	1.85
K-2291	0.081	K-2309	0.066
K-2292	0.074	K-2310	0.059
K-2293	0.28	K-2311	0.053
K-2294	0.062	K-2312	0.08
K-2295	1.36	K-2314	0.29
K-2296	0.22	S-16	0.11
K-2297	0.23	S-52	0.16
K-2298	0.34	S-64	0.098
K-2299	0.15	S-69	0.31
K-2300	0.14	S-80	0.1
K-2301	0.8	S-165	0.15
K-2302	0.5	S-193	0.066
K-2303	0.35	S-201	0.18
K-2304	0.098	S-202	0.15
K-2305	0.11	S-265	0.91

Example 531:

[0832] The compound of the present invention was administered to rats so as to examine the effects of the compound on the plasma calcium ion level and serum PTH level. The test was performed by orally administering single dose of the compound of the invention or a control compound to normal male SD rats with six animals in each group.

[0833] To the group 1 was administered as a control a 10 % cyclodextrin aqueous solution in a dose of 2.5 ml/kg. To the group 2 was administered as a reference (R)-N-(3-(2-chlorophenyl)propyl)-1-(3-methoxyphenyl)ethylamine (KRN568) dissolved in a 10 % cyclodextrin aqueous solution in a dose of 30 μmol/kg. To the group 3 was administered the compound of the present invention dissolved in a 10 % cyclodextrin aqueous solution in a dose of 30 μmol/kg, provided that 1 % sodium-CMC aqueous solution was used in place of 10 % cyclodextrin aqueous solution for the compounds marked with ** in Table 2.

[0834] Blood of each rat was collected from the tail tip before the administration and 30 minutes and 1, 2, 4, 8 and 24 hours thereafter (or at the time indicated in Table 2), and the plasma Ca^{2+} level and serum PTH level were measured. The data of the serum PTH level were statistically processed by the multiple comparison analysis in accordance with Steel's calibration by using the group 1 as the control. The results are shown in Table 2 and Figs. 46-96.

Table 2

Compound		Plasma Ca^{2+} (mmol/l)						
		0 hr	1 hr	2 hr	4 hr	8 hr	24 hr	48 hr
K-2027	mean	1.427	1.197	1.102	0.995	1.048	1.363	
	S.E.	0.010	0.053	0.027	0.027	0.024	0.013	
K-2052	mean	1.425	1.283	1.187	1.087	1.185		
	S.E.	0.015	0.012	0.007	0.016	0.006		
K-2087	mean	1.470	1.325	1.243	1.197	1.255		
	S.E.	0.008	0.015	0.009	0.012	0.008		
K-2240	mean	1.415	1.302	1.272	1.175	1.230		
	S.E.	0.009	0.038	0.022	0.027	0.003		
K-2247	mean	1.400	1.378	1.298	1.175	1.217		
	S.E.	0.016	0.014	0.018	0.018	0.016		
K-2250	mean	1.457	1.327	1.225	1.122	1.203		
	S.E.	0.014	0.030	0.022	0.010	0.019		
K-2255	mean	1.413	1.328	1.212	1.177	1.232		
	S.E.	0.020	0.013	0.019	0.009	0.012		
K-2258	mean	1.452	1.317	1.227	1.133	1.207		
	S.E.	0.009	0.015	0.026	0.031	0.014		
K-2262	mean	1.413	1.390	1.260	1.138	1.142		

		n							
		S.E.	0.020	0.009	0.021	0.017	0.020		
	K-2263	mea	1.423	1.273	1.237	1.212	1.308		
		n							
		S.E.	0.011	0.028	0.024	0.016	0.011		
	K-2264**	mea	1.403	1.335	1.203	1.013	0.998	1.182	1.240*a
		n							
		S.E.	0.015	0.019	0.019	0.019	0.021	0.027	0.017

Table 2 (cont.)

Compound		Plasma Ca^{2+} (mmol/l)						
		0 hr	1 hr	2 hr	4 hr	8 hr	24 hr	48 hr
K-2265	mean	1.425	1.430	1.363	1.260	1.218		
	S.E.	0.019	0.012	0.010	0.023	0.008		
K-2266	mean	1.417	1.368	1.222	1.065	1.045	1.370	
	S.E.	0.020	0.021	0.036	0.023	0.017	0.009	
K-2267	mean	1.417	1.347	1.212	1.027	1.022	1.312	
	S.E.	0.015	0.018	0.019	0.016	0.018	0.023	
K-2269	mean	1.450	1.152	1.140	1.097	1.173		
	S.E.	0.016	0.057	0.029	0.017	0.017		
K-2270**	mean	1.430	1.355	1.238	1.088	1.175		
	S.E.	0.012	0.014	0.019	0.016	0.020		
K-2271	mean	1.428	1.278	1.227	1.128	1.197		
	S.E.	0.012	0.017	0.017	0.023	0.022		
K-2272**	mean	1.442	1.382	1.237	1.075	1.022	1.240	
	S.E.	0.015	0.014	0.011	0.011	0.015	0.012	
K-2279	mean	1.443	1.200	1.155	1.130	1.210	1.445	
	S.E.	0.014	0.064	0.034	0.022	0.010	0.015	
K-2280	mea	1.443	1.233	1.167	1.077	1.142	1.405	

		n						
		S.E.	0.010	0.017	0.013	0.011	0.017	0.008
	K-2281	mea	1.437	1.380	1.245	1.103	0.993	1.230*b
		n						
		S.E.	0.015	0.017	0.031	0.011	0.011	0.014
	K-2282**	mea	1.435	1.425	1.298	1.168	1.078	1.230*b
		n						
		S.E.	0.016	0.019	0.015	0.017	0.010	0.014
	K-2283**	mea	1.433	1.395	1.305	1.210	1.253	
		n						
		S.E.	0.016	0.015	0.014	0.013	0.014	

Table 2 (cont.)

Compound		Plasma Ca^{2+} (mmol/l)						
		0 hr	1 hr	2 hr	4 hr	8 hr	24 hr	48 hr
K-2284	mean	1.428	1.377	1.267	1.152	1.102		
	S.E.	0.018	0.011	0.025	0.025	0.020		
K-2286	mean	1.405	1.318	1.218	1.088	1.098	1.390	1.412
	S.E.	0.017	0.015	0.018	0.021	0.018	0.008	0.014
K-2287	mean	1.403	1.180	1.042	0.955	0.950	1.200	1.392
	S.E.	0.013	0.019	0.017	0.019	0.006	0.041	0.012
K-2288	mean	1.405	1.190	1.057	0.955	0.905	1.162	1.387
	S.E.	0.012	0.018	0.020	0.018	0.009	0.020	0.015
K-2289**	mean	1.407	1.270	1.173	1.003	1.093		
	S.E.	0.013	0.018	0.022	0.017	0.025		
K-2290**	mean	1.380	1.428	1.248	1.063	1.055		
	S.E.	0.007	0.014	0.028	0.019	0.033		
K-2291**	mean	1.410	1.298	1.247	1.130	1.132		
	S.E.	0.017	0.041	0.022	0.021	0.019		
K-2292	mean	1.412	1.375	1.252	1.152	1.108		
	S.E.	0.014	0.007	0.012	0.015	0.015		
K-2293	mean	1.408	1.245	1.152	1.068	1.088		

		n					
		S.E.	0.012	0.039	0.022	0.020	0.014
	K-2294**	mea	1.410	1.357	1.255	1.117	1.022
		n					
		S.E.	0.018	0.014	0.022	0.026	0.015
	K-2296**	mea	1.410	1.340	1.195	1.113	1.083
		n					
		S.E.	0.013	0.009	0.013	0.014	0.016
	K-2297	mea	1.405	1.393	1.305	1.172	1.082
		n					
		S.E.	0.016	0.010	0.022	0.016	0.022

Table 2 (cont.)

Compound		Plasma Ca^{2+} (mmol/l)						
		0 hr	1 hr	2 hr	4 hr	8 hr	24 hr	48 hr
K-2298	mean	1.405	1.348	1.265	1.187	1.100		
	S.E.	0.015	0.015	0.030	0.024	0.017		
K-2299	mean	1.395	1.287	1.192	0.998	0.983	1.382[*c]	
	S.E.	0.015	0.013	0.021	0.019	0.014	0.013	
K-2300**	mean	1.395	1.293	1.158	0.958	1.022	1.397[*c]	
	S.E.	0.014	0.015	0.019	0.022	0.014	0.020	
K-2301	mean	1.397	1.237	1.165	1.077	1.075	1.350[*c]	
	S.E.	0.009	0.030	0.017	0.024	0.019	0.010	
K-2302**	mean	1.412	1.238	1.130	0.978	1.010		
	S.E.	0.014	0.019	0.013	0.016	0.016		
K-2303	mean	1.415	1.255	1.165	1.020	1.032		
	S.E.	0.018	0.021	0.018	0.010	0.023		
K-2304	mean	1.382	1.262	1.157	1.053	1.065		
	S.E.	0.014	0.029	0.023	0.006	0.012		
K-2305	mean	1.415	1.242	1.170	1.098	1.202		
	S.E.	0.015	0.018	0.013	0.025	0.022		
K-2309	mean	1.428	1.320	1.207	1.018	0.963	1.332[*d]	

		n					
		S.E.	0.016	0.012	0.024	0.029	0.008	0.003
	K-2310	mea	1.428	1.342	1.188	1.008	0.943	1.330*d
		n					
		S.E.	0.014	0.014	0.025	0.026	0.013	0.014
	K-2311**	mea	1.447	1.375	1.232	1.075	1.110	
		n					
		S.E.	0.014	0.011	0.012	0.016	0.034	
	KRN568	mea	1.378	1.305	1.237	1.290	1.340	
		n					
		S.E.	0.018	0.014	0.008	0.012	0.015	

NOTE: *a: 31hr, *b: 27hr, *c: 23hr, *d: 28hr

[0835] As these tables and figures clearly show, the compound of the present invention was able to lower the plasma Ca^{2+} level and serum PTH level in vivo.

Claims

1. A compound having the formula:

$$Ar_1\text{-}[CR^1R^2]_p\text{-}X\text{-}[CR^3R^4]_q\text{-}[CR^5R^6]\text{-}NR^7\text{-}[CR^8R^9]\text{-}Ar_2$$

wherein:

Ar_1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl)amino;
X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;
R^1, R^2, R^3, R^4, R^5, R^6, R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, trihalomethyl, aryl, heteroaryl, heteroalicyclic, halogen, hydroxy, alkoxy, thioalkoxy, aryloxy, thioaryloxy, carbonyl, thiocarbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, cyano, nitro, amino and $NR^{10}R^{11}$; wherein,
R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, carbonyl, trihaloacetyl, sulfonyl, trihalomethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen;
any two adjacent "R" groups may be combined to form five- or six-member fused cycloalkyl groups;
R^7 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, halogen, cyano, hydroxy, alkoxy, O-carboxyl, trihaloacetyl and trihalomethanesulfonyl;
Ar_2 is selected from the group consisting of aryl and heteroaryl;
p is an integer of from 0 to 6, inclusive; and,
q is an integer of from 0 to 14, inclusive;
or a pharmaceutically acceptable salt or hydrate of said compound.

2. The compound, salt or hydrate of claim 1 wherein: R^5 is selected from the group consisting of hydrogen, unsubstituted lower alkyl and lower alkyl substituted with one or more halogens; and R^6 and R^7 are hydrogen.

3. The compound, salt or hydrate of claim 2 wherein R^5 is hydrogen.

4. The compound, salt or hydrate of claim 3 wherein R^1, R^2, R^3 and R^4 are hydrogen.

5. The compound, salt or hydrate of claim 4 wherein R^8 and R^9 are independently selected from the group consisting of hydrogen, unsubstituted alkyl, lower alkyl substituted with one or more halogens, unsubstituted alkenyl, lower alkenyl substituted with one or more halogens, unsubstituted alkynyl, alkynyl substituted with one or more halogens and, combined, unsubstituted cycloalkyl and cycloalkeny.

6. The compound, salt or hydrate of claim 5 wherein Ar_1 is selected from the group consisting of phenyl, naphthyl, indolyl, fluorenyl, dibenzofuranyl, carbazolyl, benzoxazole-2-yl, benzthiazole-2-yl, pyridin-4-yl, quinolin-2-yl and dibenzylamino.

7. The compound, salt or hydrate of claim 6 wherein Ar_1 is optionally substituted with one or more groups independently selected from the group consisting of halogen, unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, hydroxy, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, unsubstituted phenyl and phenyl substituted with one or more groups selected from unsubstituted lower alkyl, halogen, trihalomethyl and trihalomethoxy; R^8 is hydrogen; and R^9 is unsubstituted lower alkyl.

8. The compound, salt or hydrate of claim 7 wherein Ar_2 is selected from the group consisting of phenyl, naphthyl, quinolin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrrol-2-yl and pyrrol-3-yl.

9. The compound, salt or hydrate of claim 8 wherein: Ar_2 is optionally substituted with one or more groups independently selected from the group consisting of unsubstituted medium alkyl, medium alkyl substituted with one or more halogens, hydroxy, unsubstituted medium alkoxy, medium alkoxy substituted with one or more halogens, halogen, unsubstituted benzyloxy, benzyloxy substituted with one or more groups independently selected from halogen and methyl.

10. The compound, salt or hydrate of claim 6 or 7 wherein Ar_2 is selected from the group consisting of optionally substituted phenyl and optionally substituted naphthyl.

11. The compound, salt or hydrate of claim 9 or 10 wherein Ar_1 is phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, halogen, trihalomethyl, unsubstituted lower alkoxy, trihalomethoxy, trihaloacetyl and nitro.

12. The compound, salt or hydrate of claim 11 wherein p is 1 and Ar_2 is selected from the group consisting of 3-methoxyphenyl and unsubstituted naphthyl.

13. The compound, salt or hydrate of claim 12 wherein q is an integer of from 1 to 8, inclusive.

14. The compound, salt or hydrate of claim 11 wherein p is 0, Ar_2 is 3-methoxyphenyl or unsubstituted naphthyl, and q is an integer of from 1 to 8, inclusive.

15. The compound, salt or hydrate of claim 14 wherein R^8 is hydrogen and R^9 is methyl.

16. The compound, salt or hydrate of claim 15 wherein X is selected from the group consisting of oxygen and sulfur.

17. The compound, salt or hydrate of claim 16 wherein said compound is the R enantiomer.

18. A prodrug of any of said compounds of claims 1 through 17, inclusive.

19. A compound of the formula:

$$Ar_3\text{-}(CHR^{12})_r\text{-}Q\text{-}(CH_2)_s\text{-}CHR^{13}\text{-}NH\text{-}CR^{14}R^{15}\text{-}Ar_4$$

wherein:

Ar_3 is selected from the group consisting of aryl and heteroaryl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkenyl, lower alkenyl substituted with one or more halogens, halogen, hydroxy, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, unsubstituted lower thioalkoxy, nitro, formyl, acetoxy, acetyl, $-CH_2OH$, $CH_3CH(OH)-$, $-C(=O)NH_2$, cyano, $-N(\text{lower alkyl})_2$, phenyl, phenoxy, benzyl, benzyloxy, methylenedioxy, ethylenedioxy, α, α-dimethylbenzyl, and $-OCH_2COOH$;

Ar_4 is selected from the group consisting of aryl and heteroaryl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkenyl, lower alkenyl substituted with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, hydroxy, lower thioalkoxy, halogen, methylenedioxy, ethylenedioxy, acetoxy, $-OCH_2COOH$, $-C(=O)NH_2$, cyano, and $-CH_2OH$;

r is an integer of from 0 to 6, inclusive;

s is an integer of from 0 to 14, inclusive;

Q is selected from the group consisting of oxygen, sulfur, carbonyl and -NH-;

R^{13} is hydrogen or lower alkyl; and

R^{14} and R^{15} are independently selected from the group consisting of hydrogen, alkyl and, combined, cycloalkyl and cycloalkenyl;

or a pharmaceutically acceptable salt or hydrate of said compound.

20. The compound, salt, hydrate or prodrug of claim 19 wherein:

Ar_3 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and optionally substituted naphthyl;

Ar_4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and optionally substituted naphthyl;

R^{14} is selected from the group consisting of unsubstituted lower alkyl and lower alkyl substituted with one or more halogens; and

R^{15} is hydrogen.

21. The compound, salt, hydrate or prodrug of claim 20 wherein:

Ar_3 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and unsubstituted naphthyl;

Ar_4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and unsubstituted naphthyl;

r is 0 or 1, wherein when r is 1, R^{12} is hydrogen.

22. The compound, salt or hydrate of claim 21 wherein s is and integer of from 1 to 8, inclusive.

23. The compound, salt or hydrate of claim 21 wherein s is and integer of from 1 to 5, inclusive.

24. The compound, salt or hydrate of claim 23 wherein Q is selected from the group consisting of oxygen and sulfur.

25. The compound, salt or hydrate of claim 24 wherein R^{13} is selected from the group consisting of hydrogen and methyl.

26. The compound, salt or hydrate of claim 25 wherein R^{13} is hydrogen and R^{14} is methyl.

27. The compound, salt or hydrate of claim 26 wherein said compound is the R enantiomer.

28. A prodrug of any of said compounds of claims 19 through 27, inclusive.

29. A compound of the formula:

$$Ar_5\text{-}(CHR^{16})_t\text{-}W\text{-}(CH_2)_u\text{-}CHR^{17}\text{-}NH\text{-}CH(R^{18})\text{-}Ar_6$$

wherein:

Ar_5 is aryl, dicyclic or tricyclic heteroaryl, arylmethyl(arylmethyl)amino, heteroarylmethyl(heteroarylmethyl)amino or arylmethyl(heteroarylmethyl)amino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, unsubstituted lower alkenyl, halogen, hydroxy, unsubstituted lower alkoxy, unsubstituted lower thioalkoxy, lower alkyl substituted with one or more halogens, lower alkenyl substituted with one or more halogens, lower alkoxy substituted with one or more halogens, nitro, formyl, acetoxy, acetyl, $-CH_2OH$, $CH_3CH(OH)$-, $-C(=O)NH_2$, cyano, -N(unsubstituted lower alkyl)$_2$, phenyl, phenoxy, benzyl, benzyloxy, α, α -dimethylbenzyl, methylenedioxy, ethylenedioxy and $-OCH_2COOH$;
Ar_6 is aryl or dicyclic or tricyclic heteroaryl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halogens, unsubstituted lower alkenyl, lower alkenyl substituted with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, halogen, hydroxy, unsubstituted lower thioalkoxy, lower thioalkoxy substituted with one or more halogens, benzyloxy, methylenedioxy, ethylenedioxy, acetoxy, $-OCH_2COOH$, $-C(=O)NH_2$, cyano, and $-CH_2OH$;
t is 0 or 1;
u is an integer of from 0 to 11, inclusive;
W is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;
R^{16} and R^{17} are H or unsubstituted lower alkyl; and
R^{18} is unsubstituted lower alkyl;
or a pharmaceutically acceptable salt or hydrate of said compound.

30. The compound, salt or hydrate of claim 29 wherein:

Ar_5 is phenyl, indole, benzothiazole, benzoxazole, dibenzofuran, carbazole, pyridine, fluorene, quinoline, naphthalene, chromenone, tetrahydrobenzothiazepine, dibenzylamino, benzyl(naphthylmethyl)amino, benzyl(pyridylmethyl)amino, thienylmethyl(benzyl)amino, furylmethyl(benzyl)amino or N-alkylpyrrolylmethyl(benzyl)amino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl; and
Ar_6 is thiophene, furan, pyrrole, phenyl, naphthalene, pyridine, pyrazine or thiazole optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens, lower alkoxy substituted with one or more halogens, hydroxy and benzyloxy optionally substituted with halogen or methyl;
R^{16} and R^{17} are H or methyl; and
R^{18} is methyl.

31. The compound, salt or hydrate of claim 30 wherein:

Ar_5 is phenyl, benzothiazole, benzoxazole, dibenzofuran, carbazole, pyridine, quinoline or naphthalene optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens;
Ar_6 is phenyl or naphthalene, wherein said phenyl is optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens and benzyloxy optionally substituted with halogen or methyl:
t is 0;
u is an integer of from 1 to 8, inclusive;
W is sulfur; and
R^{17} is H.

32. The compound, salt or hydrate of claim 31 wherein:

Ar_5 is selected from the group consisting of phenyl optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens;
Ar_6 is 3-methoxyphenyl or α-naphthyl; and
u is an integer of from 2 to 6, inclusive.

33. The compound, salt or hydrate of claim 30 wherein:

Ar_5 is dibenzylamino, benzyl(naphthylmethyl)amino or benzyl(pyridylmethyl)amino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens;
Ar_6 is naphthyl or methoxyphenyl;
t is zero;
u is an integer of from 0 to 8, inclusive;
W is carbonyl; and
R^{17} is H.

34. The compound, salt or hydrate of claim 33 wherein:

Ar_5 is dibenzylamino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, halogen, unsubstituted lower alkoxy, lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens;
Ar_6 is 3-methoxyphenyl or α-naphthyl; and
u is 1.

35. The compound, salt or hydrate claimed in any one of claims 29-34 wherein said compound is the R enantiomer.

36. (R)-N-[1-(1'-naphthyl)ethyl]-2-(2',5'-dichorophenylthio)ethylamine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[[4-(trifluoromethoxy)phenyl]thio}pentyl)amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[4-(trifluoromethoxy)phenyl]thio}butyl)amine, N-{4-[(2,4-dimethylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[[4-(trifluoromethyl)phenyl]thio}pentyl)amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-{4-[(2,4,5-trichlorophenyl)thio]butyl}amine, N-{5-[(4-chlorophenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{5-[(2,4-dimethylphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[4-(trifluoromethyl)phenyl]thio}butyl)amine, N-{4-[(4-methylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{4-[(4-chlorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(6-[[4-(trifluoromethoxy)phenyl]thio}hexyl)amine, N-{5-[(4-methoxyphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-{5-[(2,4,5-trichlorophenyl)thio])pentyl}amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio}butyl)amine, N-{5-[(2,5-dichlorophenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{5-[(4-fluorophenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{6-[(4-chlorophenyl)thio]hexyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{4-[(3-methoxyphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{5-[(4-methylphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{4-[(2,5-dichlorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio}pentyl)amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(7-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio}heptyl)amine, N-[[4-(5-ethoxy-1,3-benzothiazol-2-yl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[[5-(3-methoxyphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(3-[[4(trifluoromethyl)phenyl]thio}propyl)amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[3-(trifluoromethyl)phenyl]thio}butyl)amine, N-{4-[(4-fluorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, , N1-(4-methylbenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1,N1-di(4-methylbenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(3,4-dichlorobenzyl)-N1-(4-methoxybenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(4-methylbenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(4-chlorobenzyl)-N1-(4-methoxybenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(4-chlorobenzyl)-N1-(3,4-dichlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(3,4-dichlorobenzyl)-N1-(4-methylbenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1,N1-di[4-(trifluoromeths-

oxy)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(4-chlorobenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(4-methoxybenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1,N1-di[4-(trifluoromethyl)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1,N1-di(4-chlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1,N1-di(4-methoxybenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-benzyl-N1-(3,4-dichlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(4-chlorobenzyl)-N1-(2-naphthylmethyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(2-chlorobenzyl)-N1-(4-chlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-benzyl-N1-(4-chlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, N1-(4-chlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, or N1,N1-di(3,4-dichlorobenzyl)-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propanamide, or a salt or hydrate thereof.

37. A pharmaceutical composition comprising said compound, salt or hydrate of any of claims 1 through 36, inclusive.

38. A method of treating a patient comprising administering to said patient a therapeutically effective amount of one or more of said compounds of said claims 1 through 37.

39. The method of claim 38 wherein said patient is suffering from a disease or disorder characterized by either or both of (1) abnormal calcium homeostasis and, (2) an abnormal amount of an intracellular or extracellular messenger whose production can be affected by calcium receptor activity.

40. A method for modulating the PTH level in a patient comprising administering to said patient an effective amount of said compound of claims 1 through 37.

41. The method of claim 40 wherein said effective amount of said compound of claims 1 through 37 reduces said PTH level in a patient.

42. The method of claim 41 wherein said patient has an abnormally high PTH level and effective amount of a compound of claims 1 through 37 reduces said PTH level in said patient to a degree sufficient to cause a decrease in plasma Ca^{2+}.

43. A method for reducing the PTH level in a patient to a level present in a normal individual comprising administering to said patient an effective amount of said compound of claims 1 through 37.

44. A method for modulating parathyroid hormone secretion in a patient comprising administering to said patient an effective amount of said compound of claims 1 through 37.

45. The method of claim 44 wherein said effective amount of said compound of claims 1 through 37 reduces said parathyroid hormone secretion in said patient.

46. The method of claim 45 wherein said patient has an abnormally high parathyroid secretion and said therapeutically effective amount of said compound of claims 1 through 37 reduces said parathyroid hormone secretion in said patient to a degree sufficient to cause a decrease on plasma Ca^{2+}.

47. A method for modulating one or more Ca^{2+} receptors activities in a cell comprising administration of one or more of said compounds, salts, or hydrates of said claims 1 through 37 to said cell.

48. The method of claim 47 wherein said cell is a parathyroid cell, a juxtaglomerular kidney cell, a proximal tubule kidney cell, a parafollicular thyroid cell, a bone osteoclast, a keratinocyte or a placental trophoblast.

49. A method for treating or preventing a disorder selected from the group consisting of hyperparathyroidism, renal osteodystrophy, hypercalcemia malignancy, osteoporosis, Paget's disease and hypertension comprising administering to a patient suffering from said disorder a therapeutically effective amount of said compound of claims 1 through 37.

50. The method of claim 49 wherein said hyperparathyroidism is primary hyperparathyroidism.

51. The method of claim 49 wherein said hyperparathyroidism is secondary hyperparathyroidism.

52. A pharmaceutical composition for treatment of primary and secondary hyperparathyroidism comprising the compound, salt or hydrate claimed in any one of claims 29-36.

53. A pharmaceutical composition for treatment of renalosteodystrophy comprising the compound, salt or hydrate claimed in any one of claims 29-36.

54. A pharmaceutical composition for treatment of hypercalcemia comprising the compound, salt or hydrate claimed in any one of claims 29-36.

55. A pharmaceutical composition for treatment of hypercalcemia malignancy comprising the compound, salt or hydrate claimed in any one of claims 29-36.

56. A pharmaceutical composition for treatment of osteoporosis comprising the compound, salt or hydrate claimed in any one of claims 29-36.

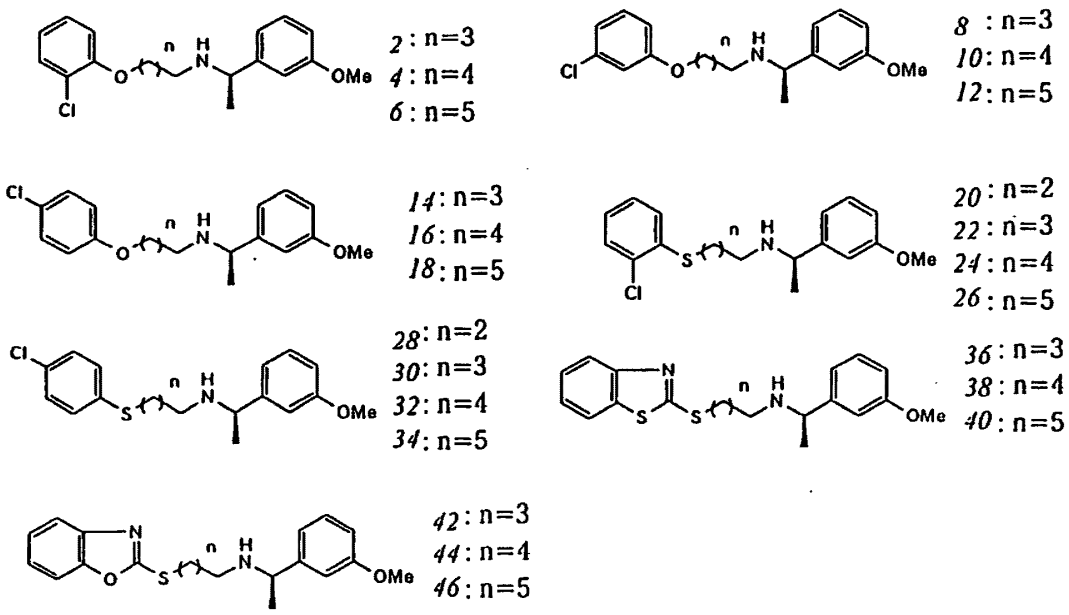
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Fig. 1

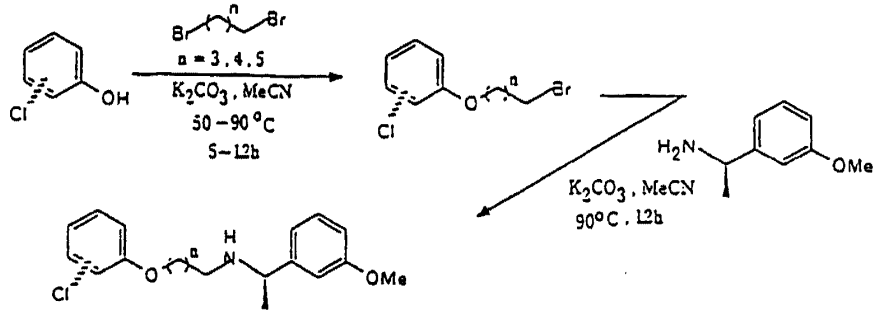

Fig. 2

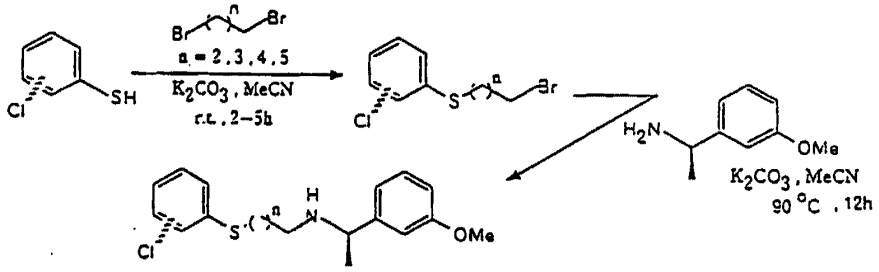

Fig. 3

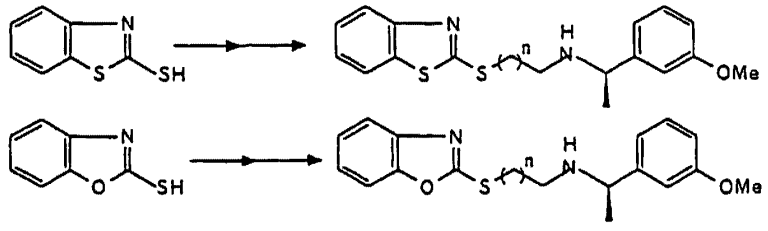

Fig. 4

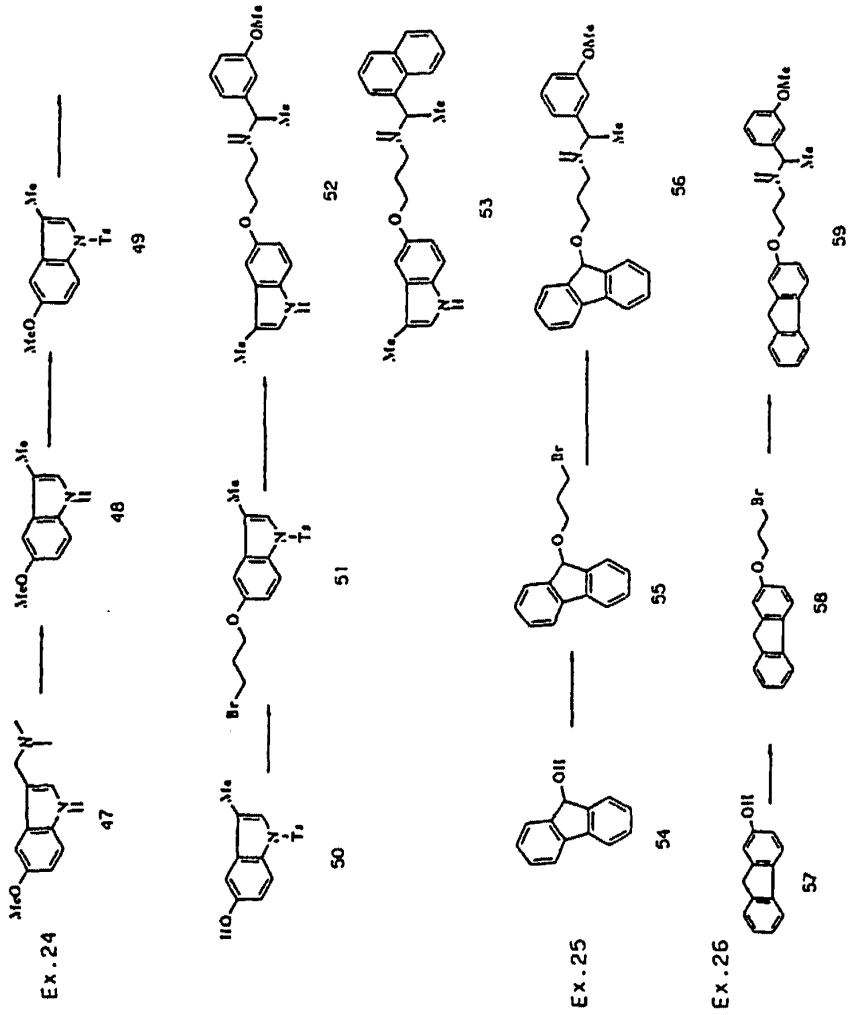

Fig. 5

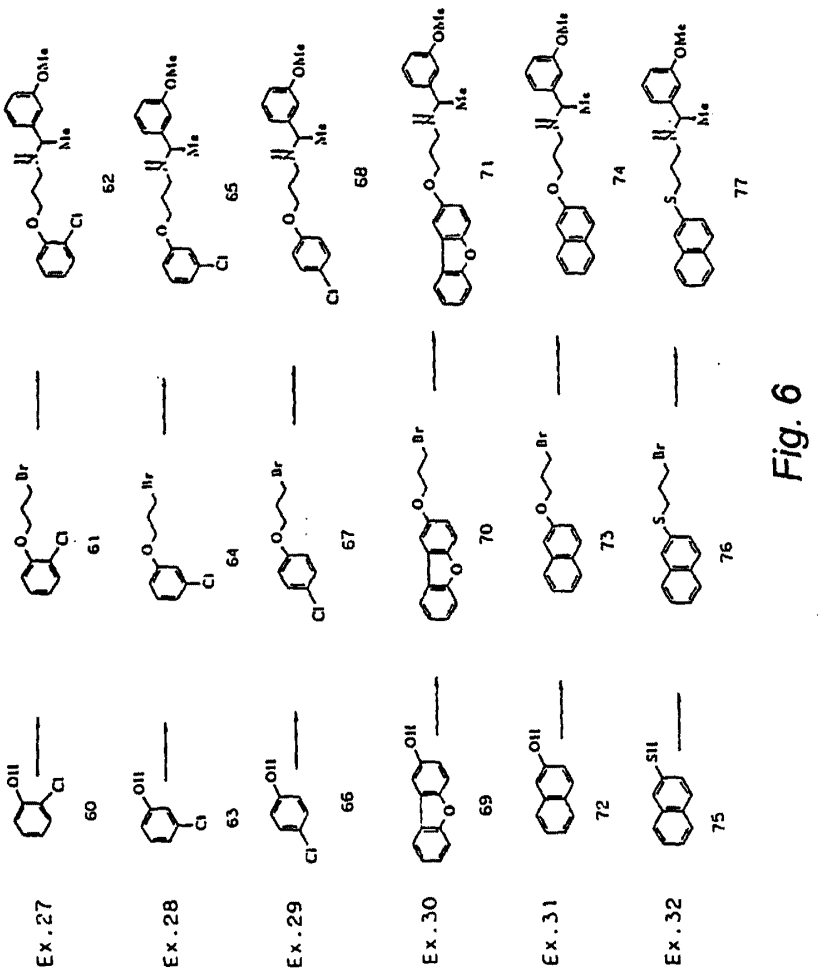

Fig. 6

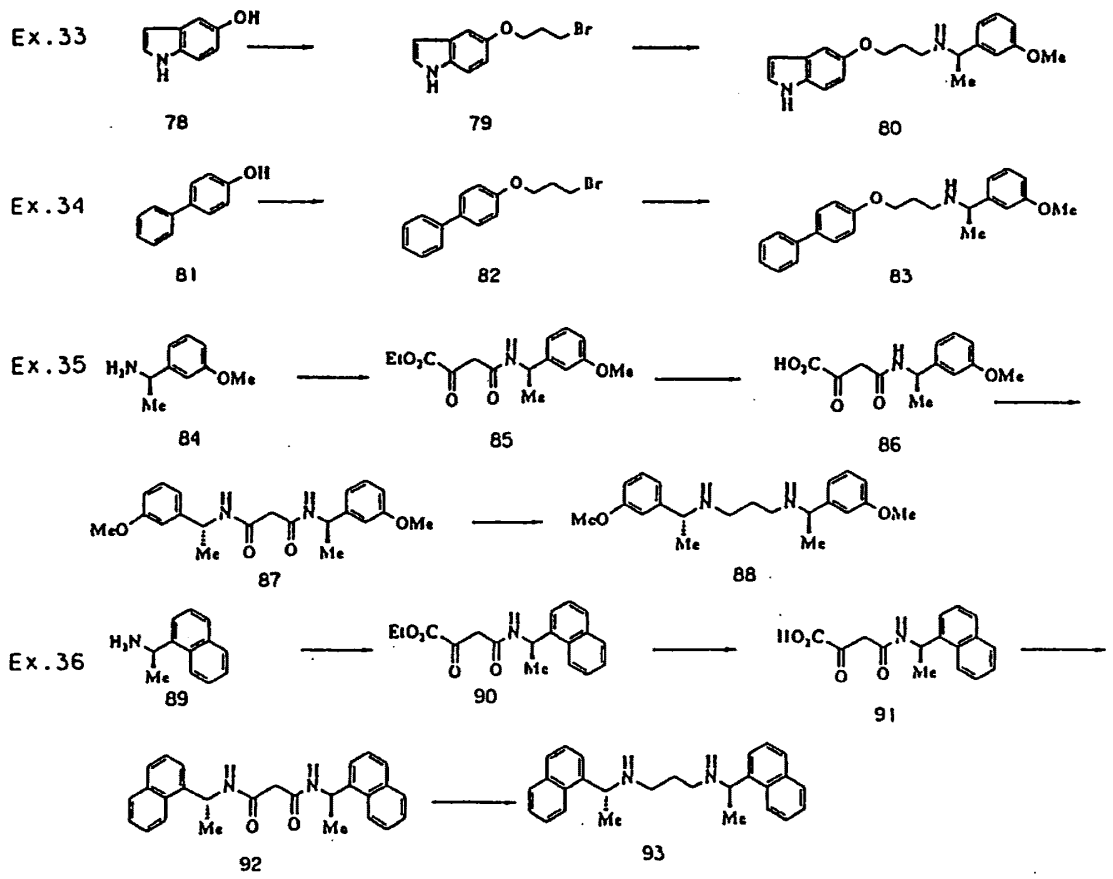

Fig. 7

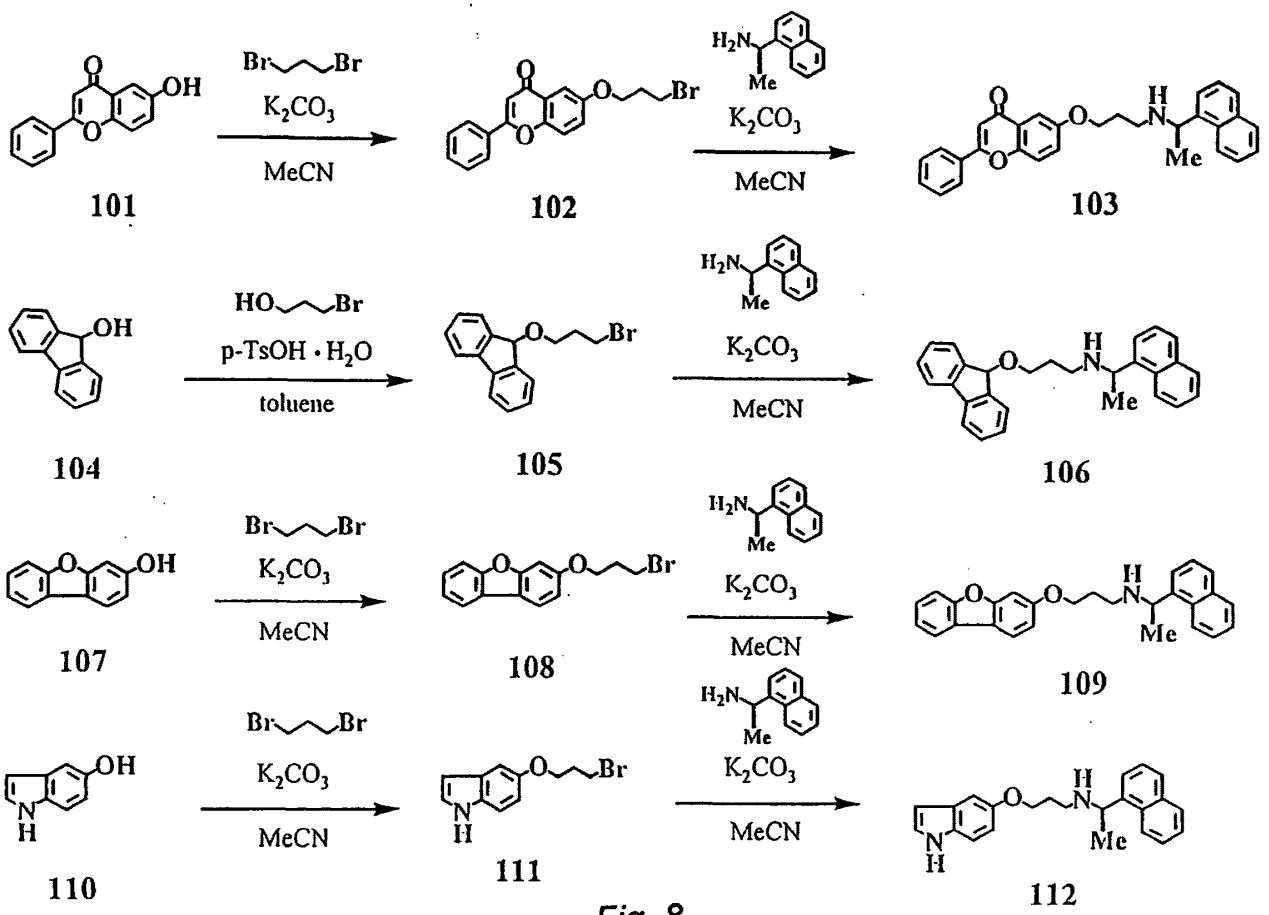

Fig. 8

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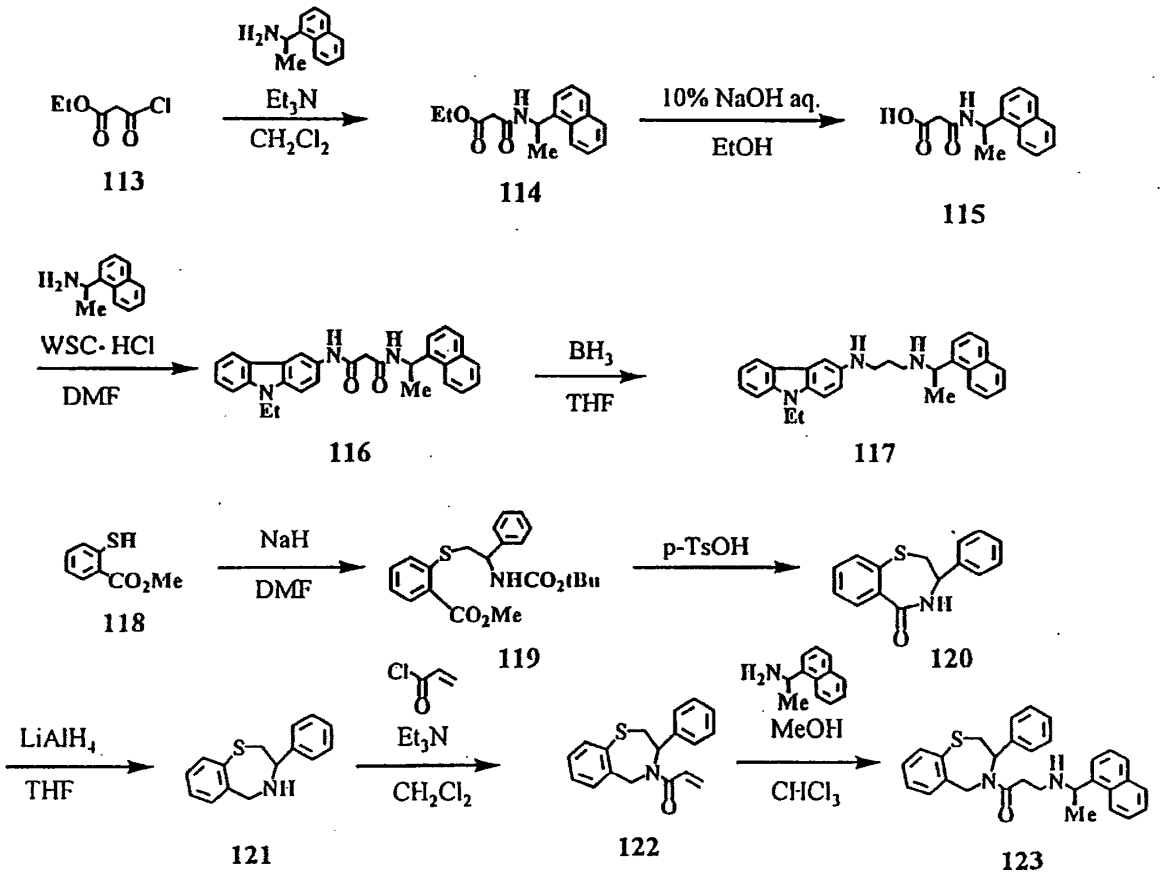
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BH3
THF
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DMF
p-TsOH
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119
120
LiAlH4
THF
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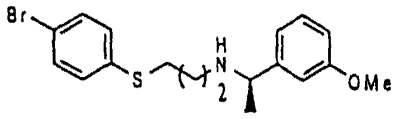
CH2Cl2
MeOH
CHCl3
121
122
123

Fig. 9



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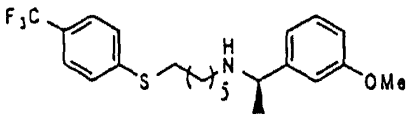

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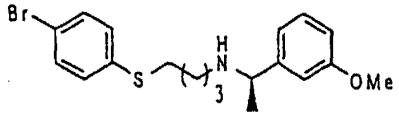

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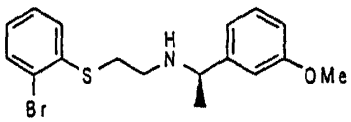

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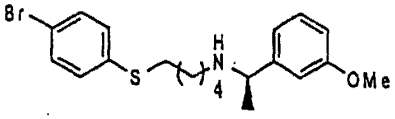

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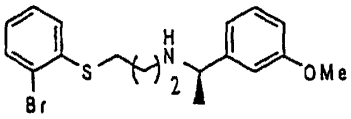

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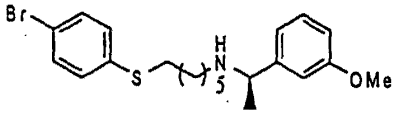

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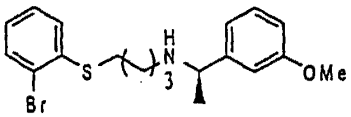

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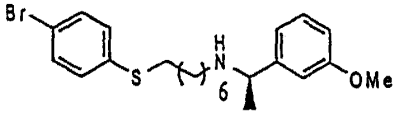

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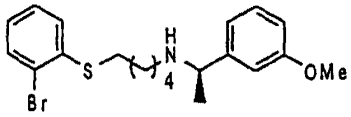

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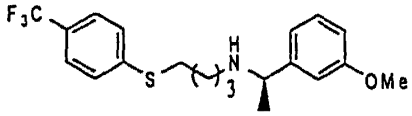

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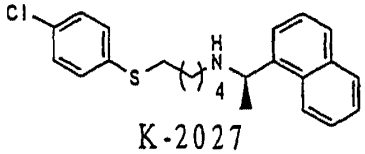

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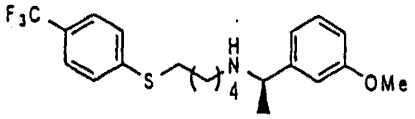

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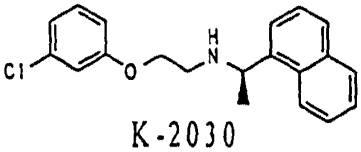

K-2030

Fig. 10

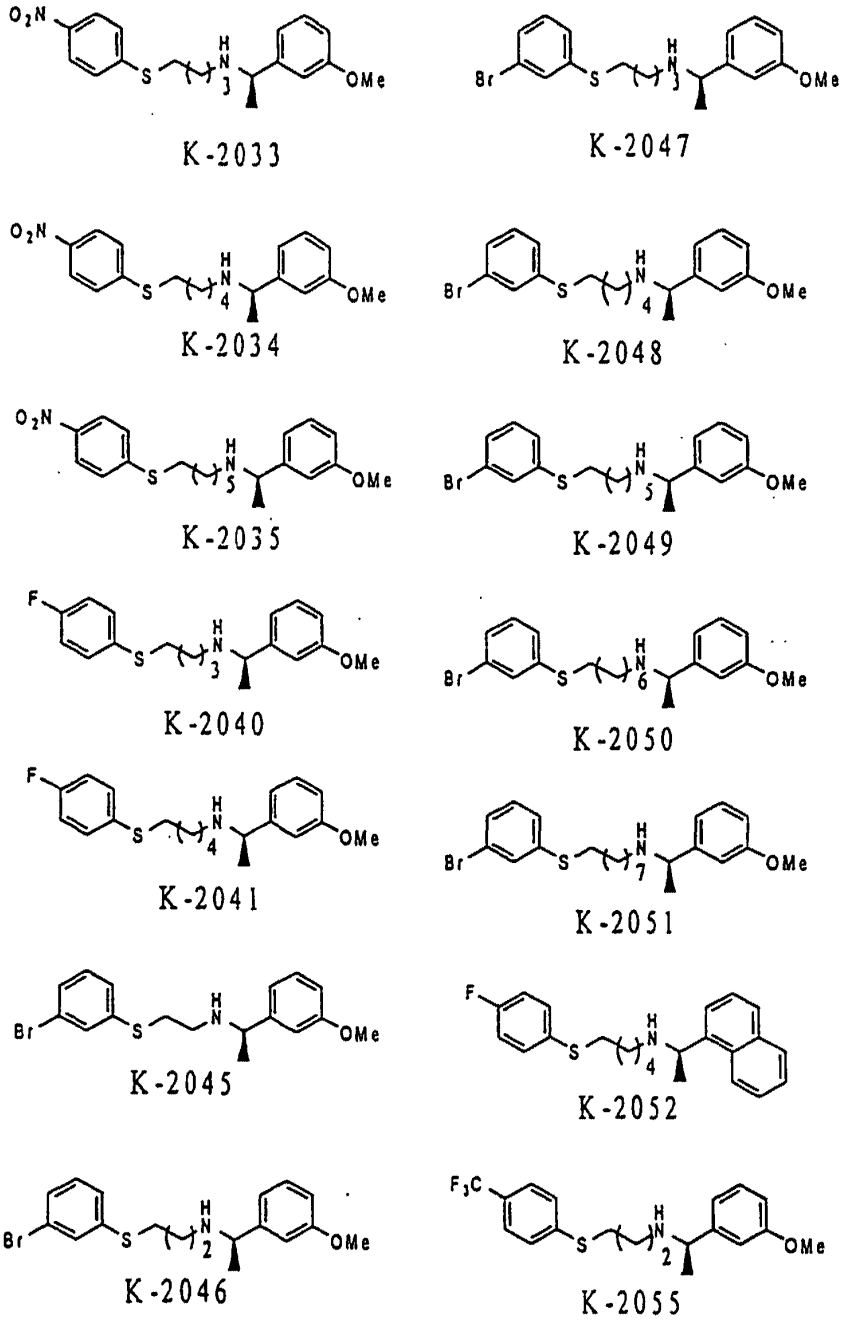
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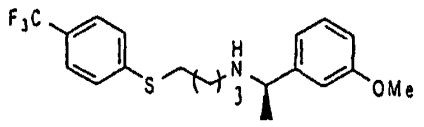
Fig. 11



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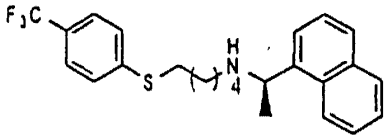

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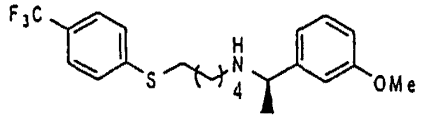

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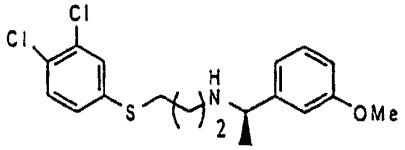

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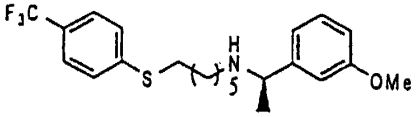

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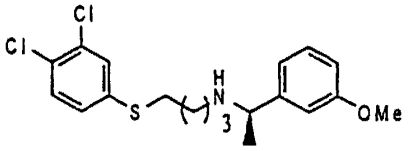

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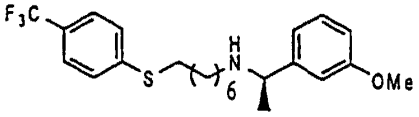
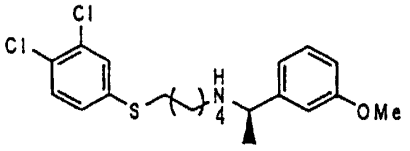
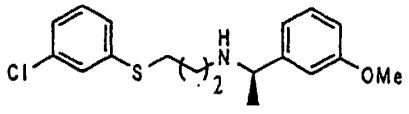


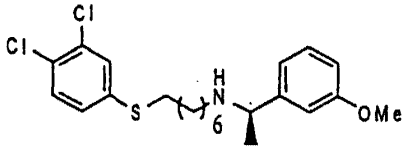
K-2059



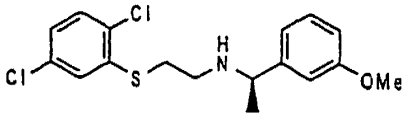
K-2080



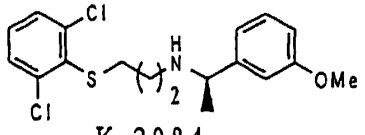
K-2061



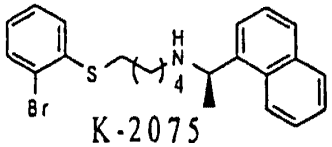
K-2082



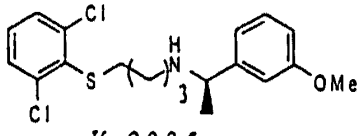
K-2066



K-2084

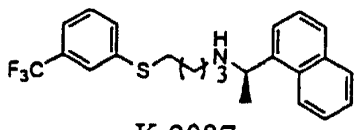


K-2075

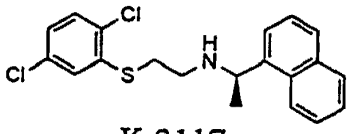


K-2085

Fig. 12



K-2087



K-2117

Fig. 13

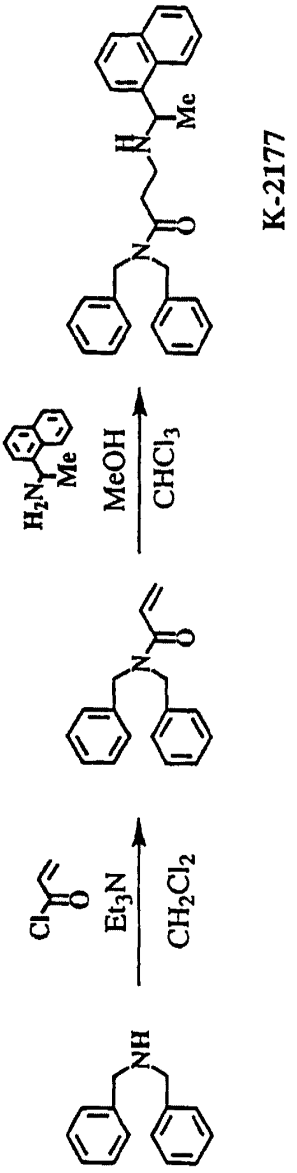
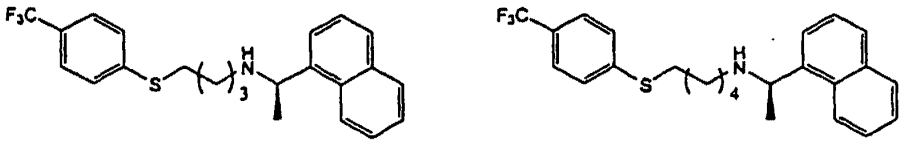


Fig. 14



K-2246 *K-2076*

Fig. 15

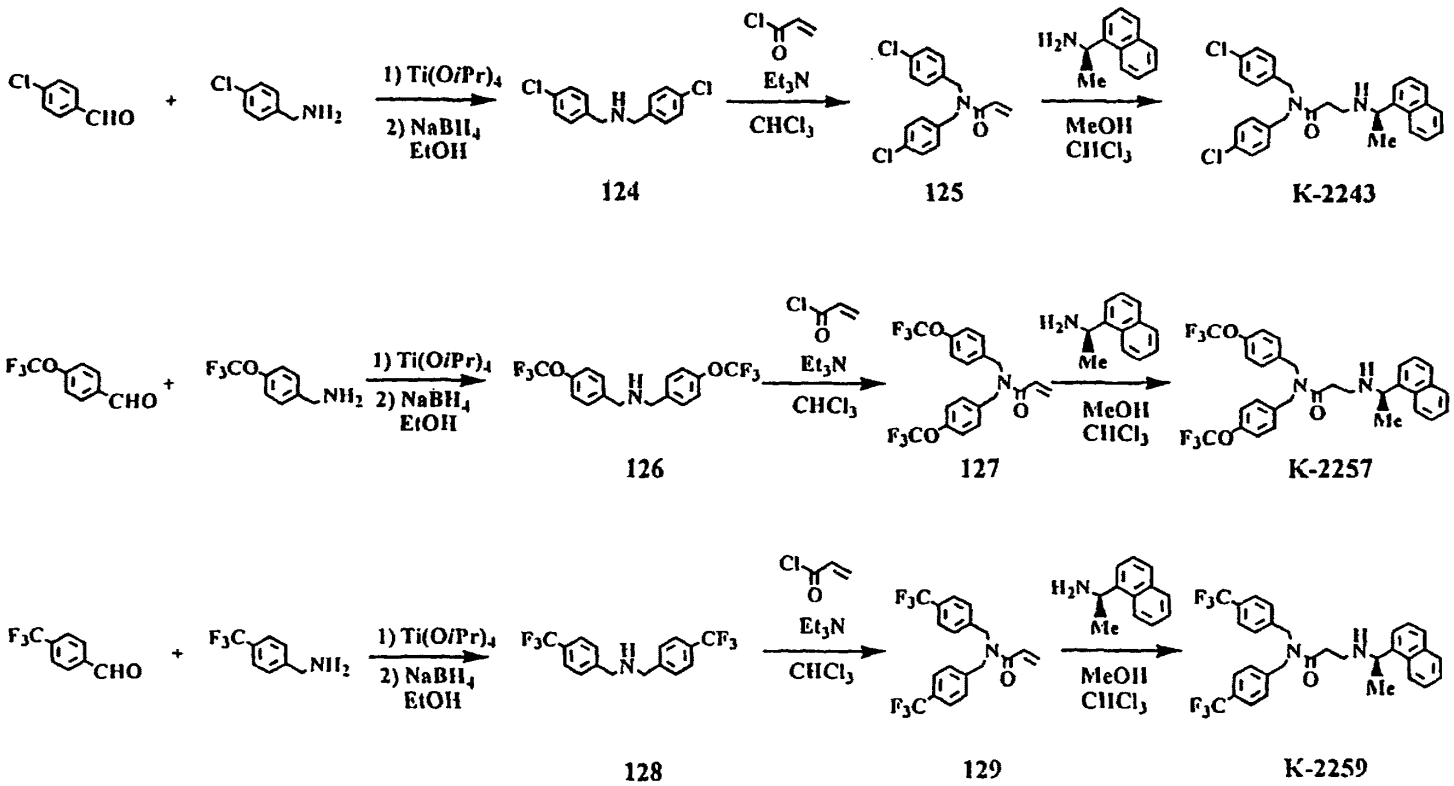

1) Ti(OiPr)4
2) NaBH4
EtOH
Et3N
CHCl3
MeOH
CHCl3
124
125
K-2243
126
127
K-2257
128
129
K-2259

Fig. 16

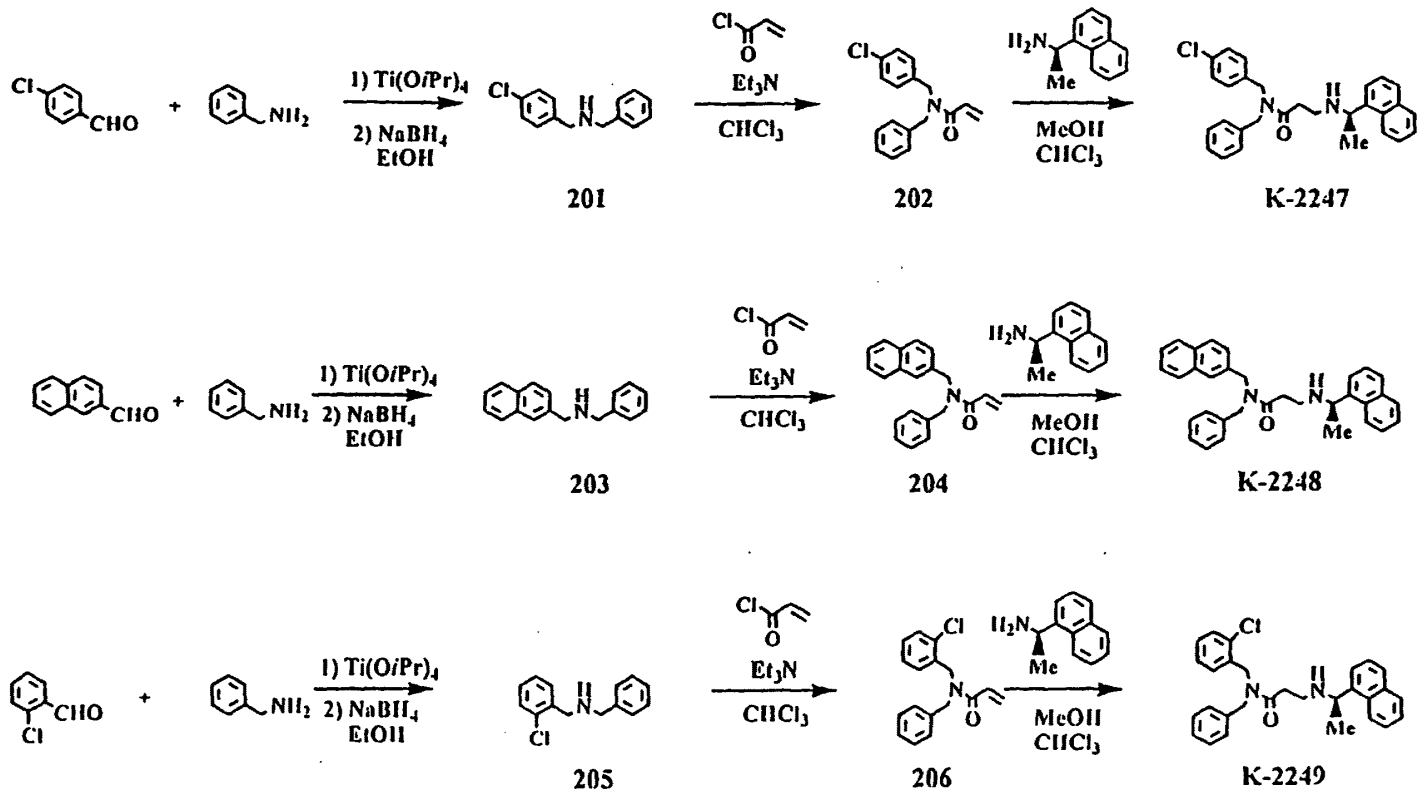

1) Ti(OiPr)4
2) NaBH4
EtOH
Et3N
CHCl3
MeOH
CHCl3
201
202
K-2247
203
204
K-2248
205
206
K-2249

Fig. 17

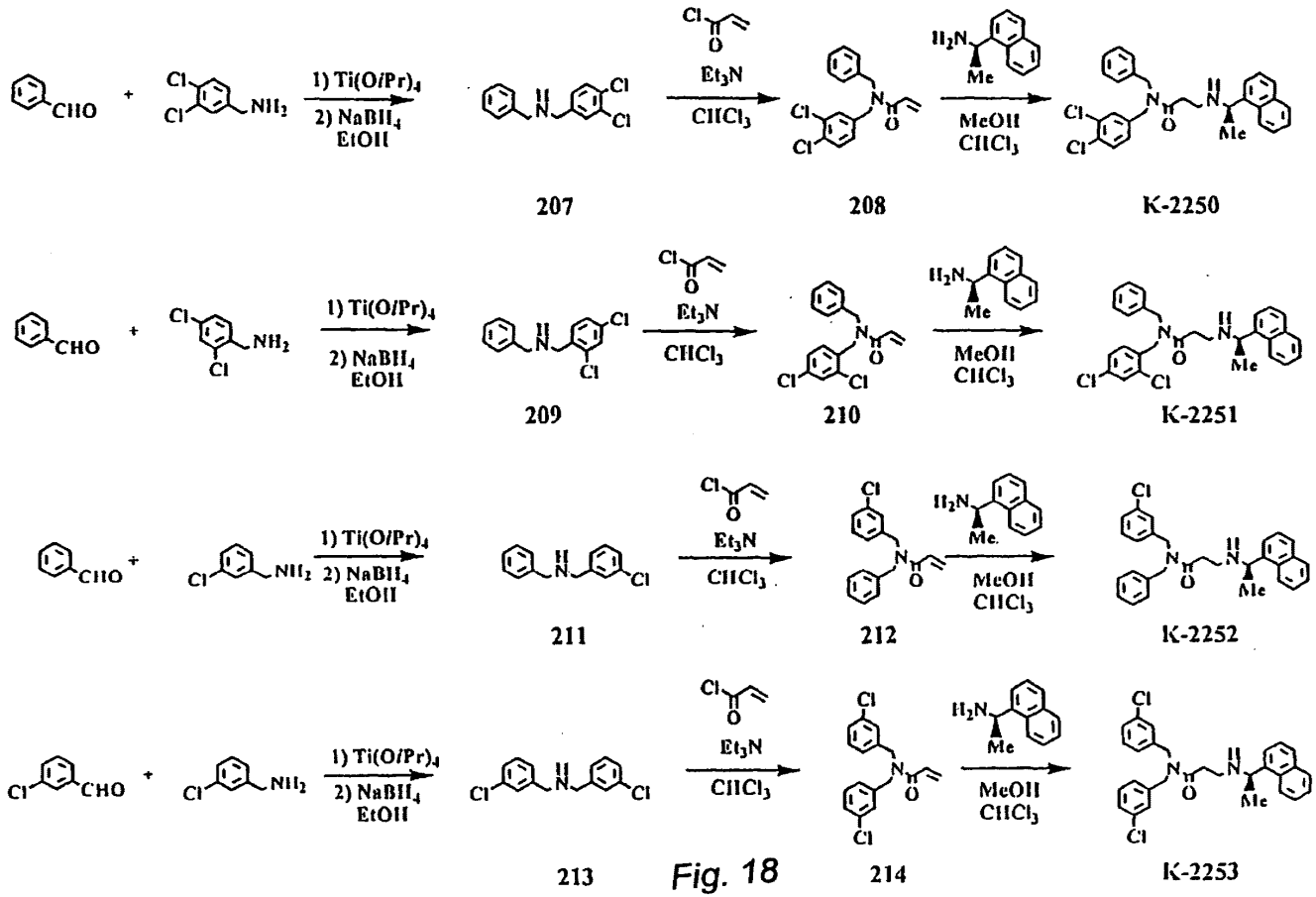

1) Ti(O/Pr)4
2) NaBH4
EtOH
Et3N
CHCl3
MeOH
CHCl3
207
208
K-2250
209
210
K-2251
211
212
K-2252
213
214
K-2253

Fig. 18

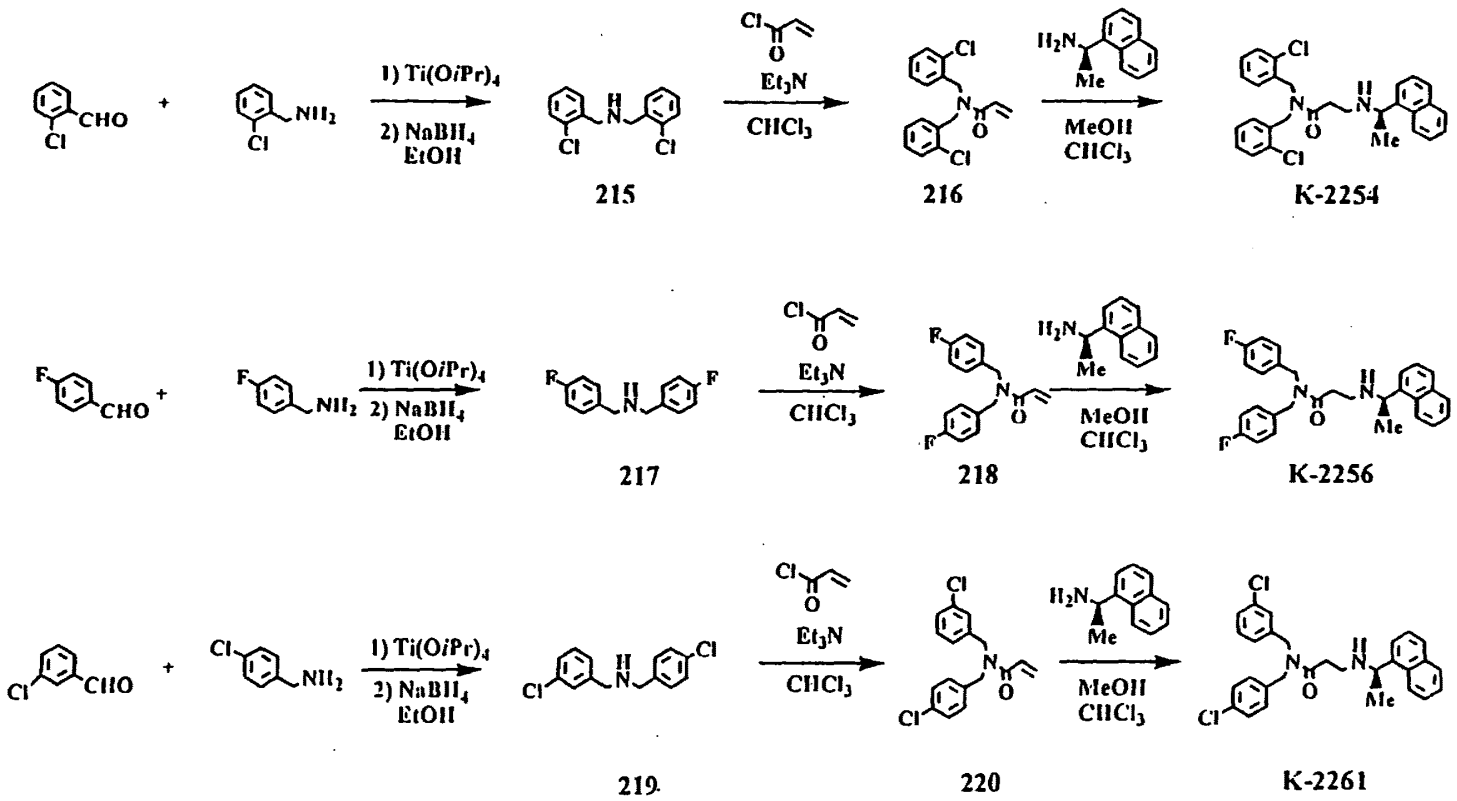

1) Ti(OiPr)4
2) NaBH4
EtOH
Et3N
CHCl3
MeOH
CHCl3
215
216
K-2254
217
218
K-2256
219
220
K-2261

Fig. 19

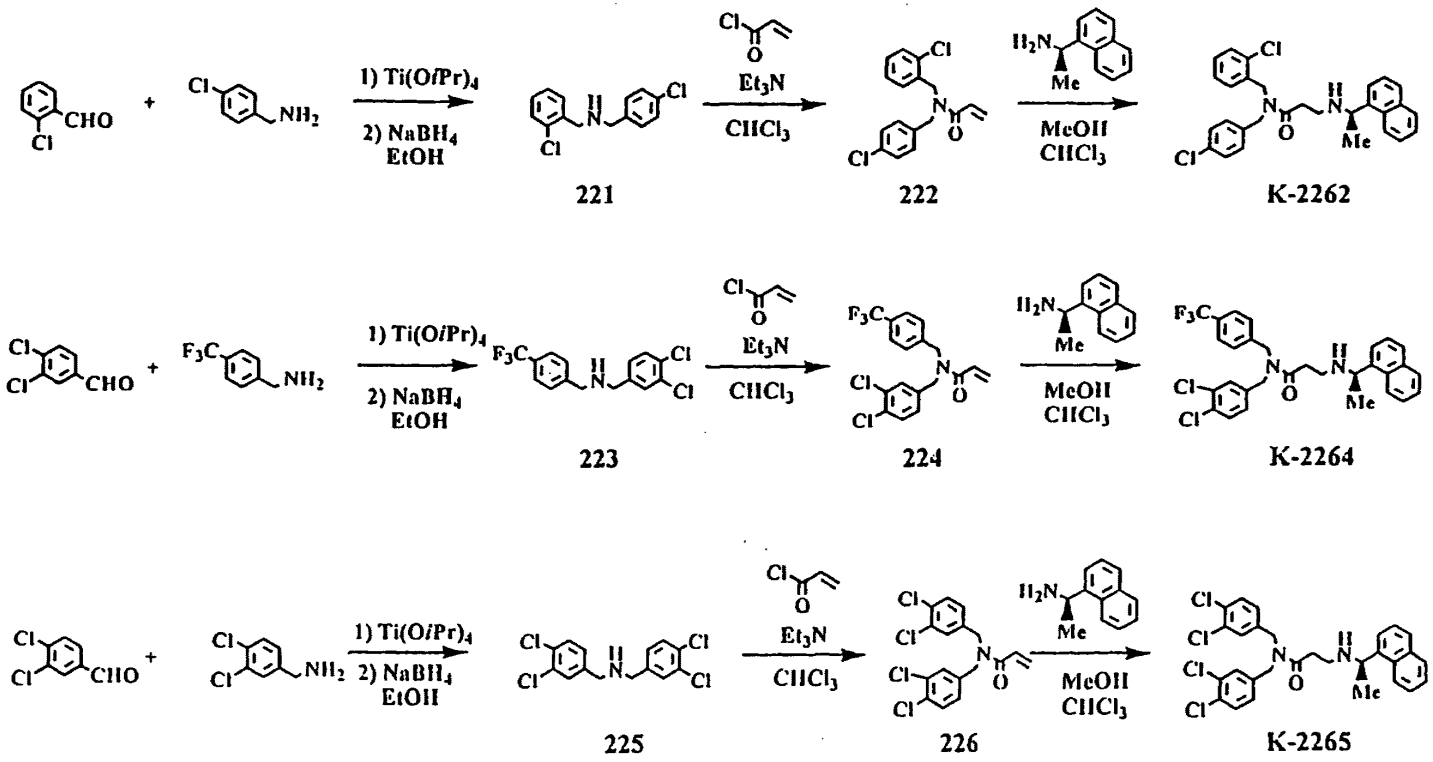

1) Ti(OiPr)4
2) NaBH4
EtOH
Et3N
CHCl3
MeOH
CHCl3
221
222
K-2262
223
224
K-2264
225
226
K-2265

Fig. 20

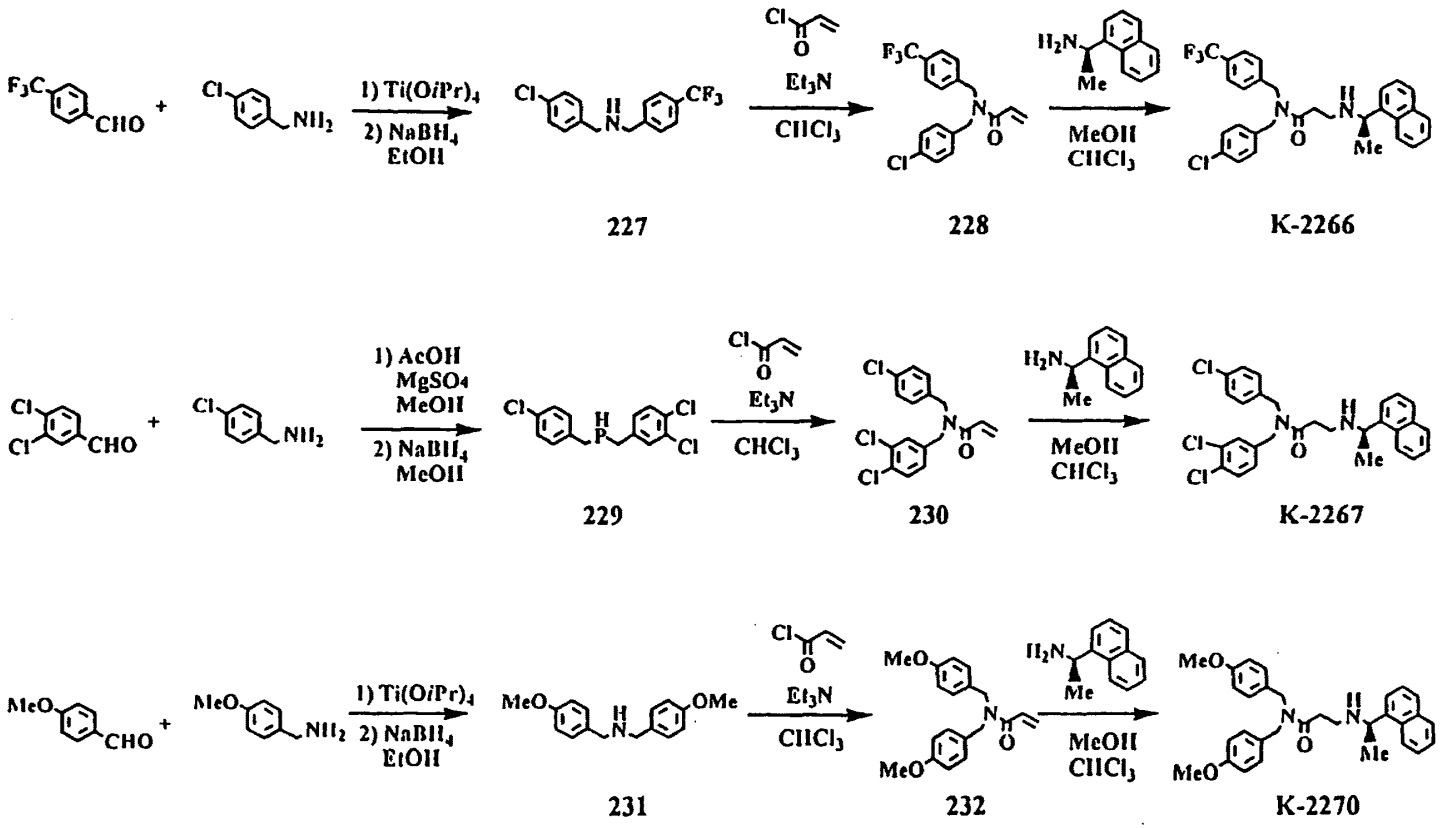


Fig. 21

EP 0 933 354 A1

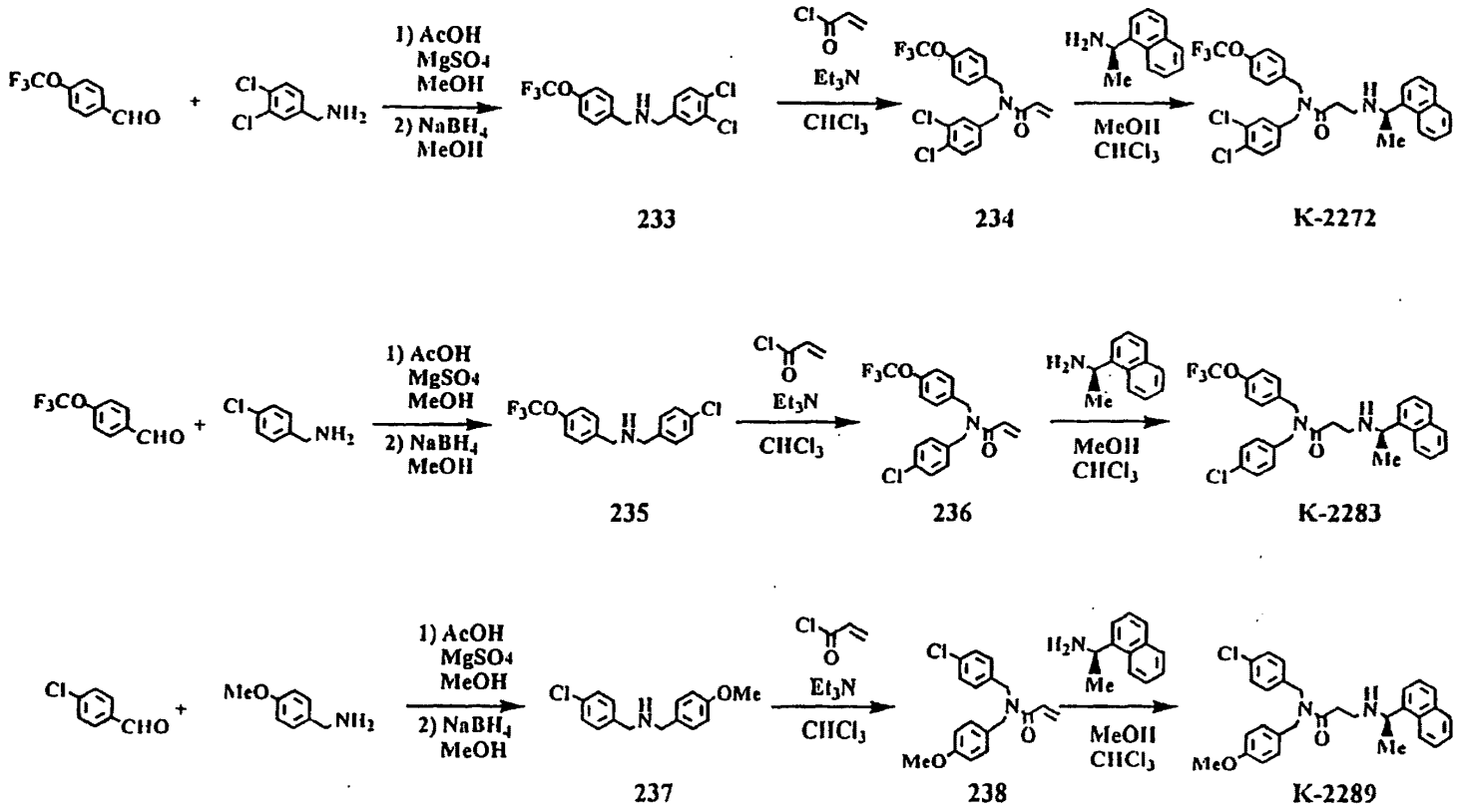

1) AcOH
MgSO4
MeOH
2) NaBH4
MeOH
Et3N
CHCl3
MeOH
CHCl3
233
234
K-2272
235
236
K-2283
237
238
K-2289

Fig. 22

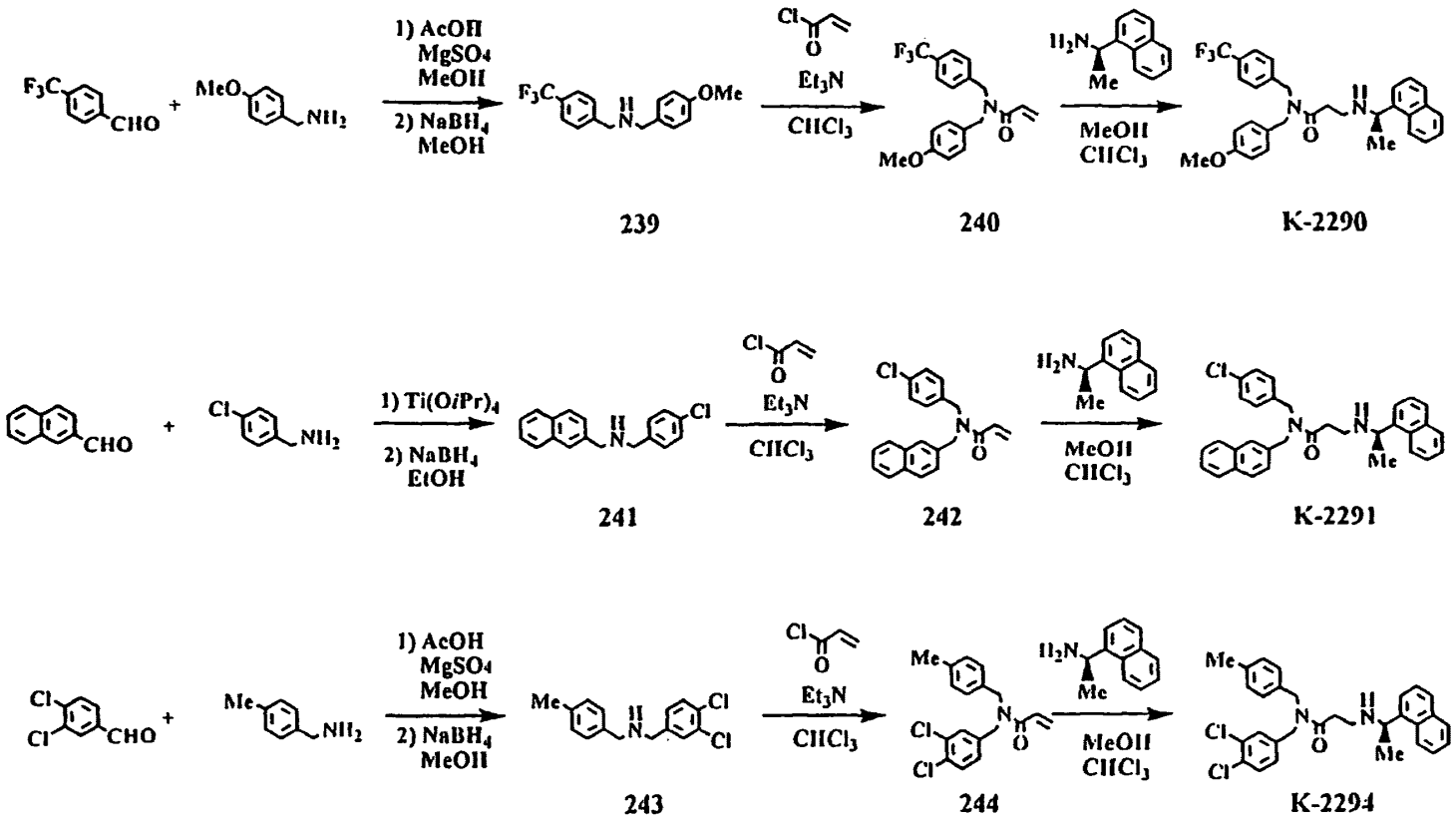

1) AcOH
MgSO4
MeOH
2) NaBH4
MeOH
Et3N
CHCl3
MeOH
CHCl3
239
240
K-2290
1) Ti(OiPr)4
2) NaBH4
EtOH
241
242
K-2291
243
244
K-2294

Fig. 23

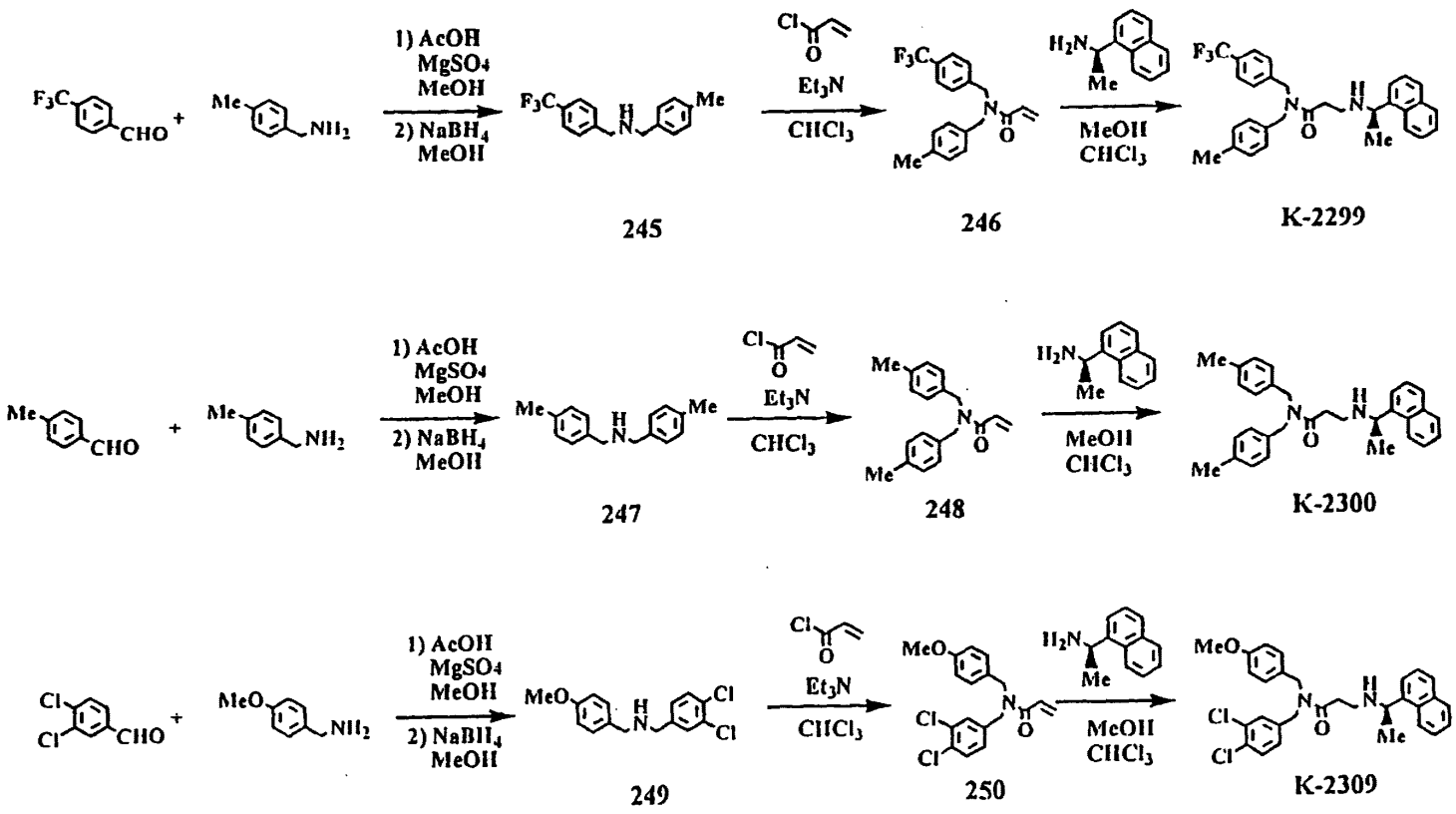

1) AcOH
MgSO4
MeOH
2) NaBH4
MeOH
Et3N
CHCl3
MeOH
CHCl3
245
246
K-2299
247
248
K-2300
249
250
K-2309

Fig. 24

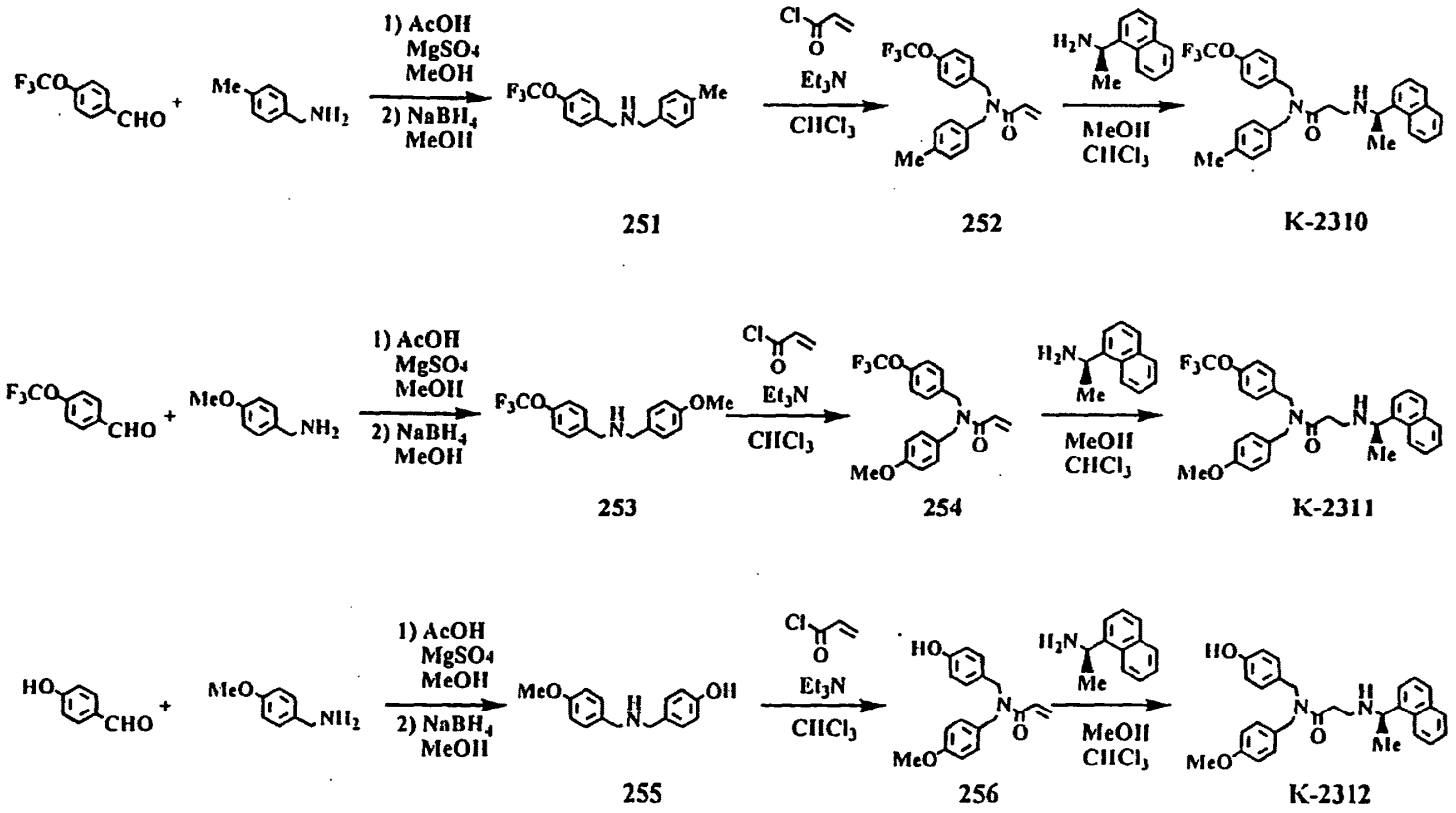
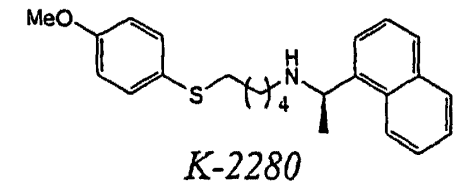
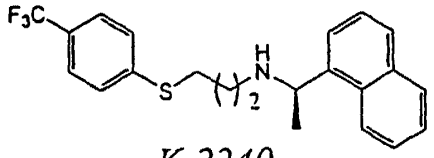

1) AcOH
MgSO4
MeOH
2) NaBH4
MeOH
Et3N
CHCl3
MeOH
CHCl3
251
252
K-2310
253
254
K-2311
255
256
K-2312

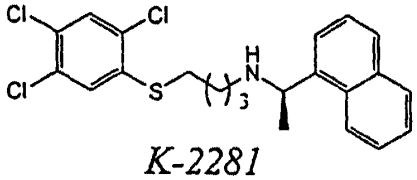
Fig. 25



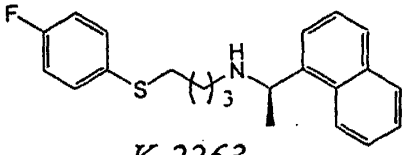
K-2280



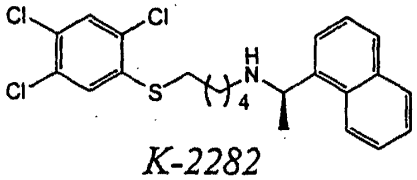
K-2240



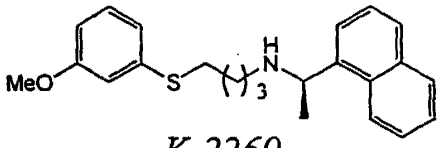
K-2281



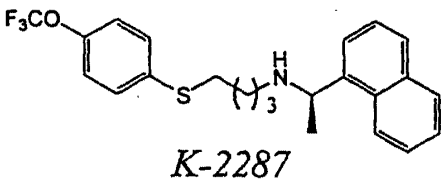
K-2263



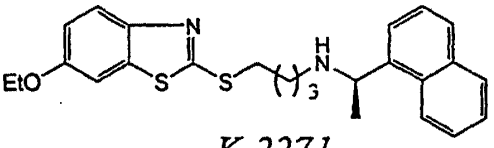
K-2282



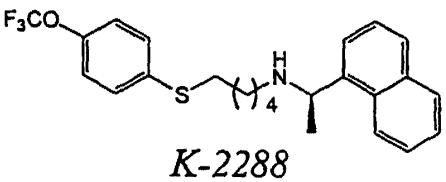
K-2269



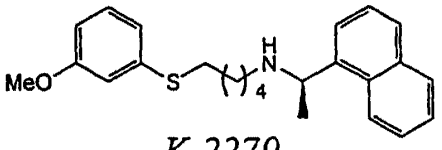
K-2287



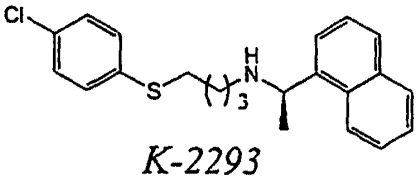
K-2271



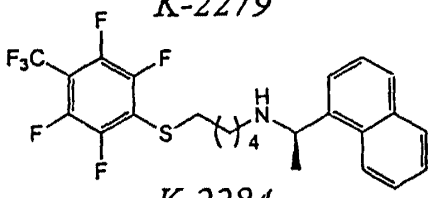
K-2288



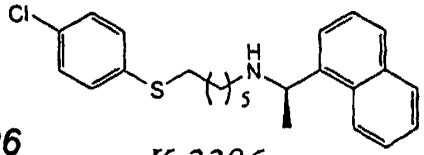
K-2279



K-2293

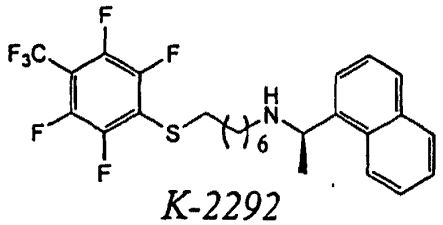


K-2284

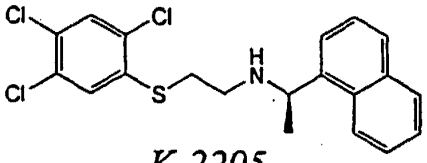


K-2286

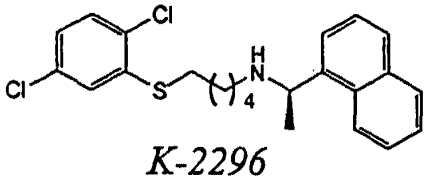
Fig. 26



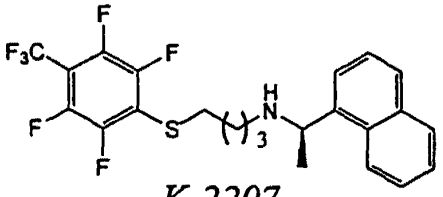
K-2292



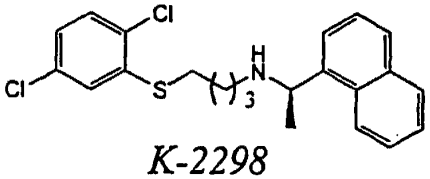
K-2295



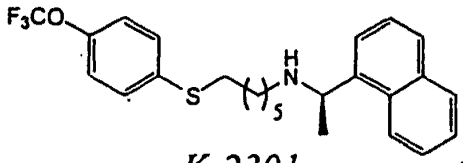
K-2296



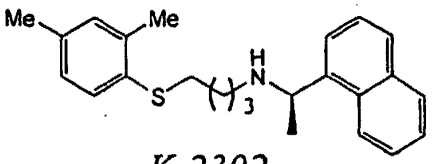
K-2297



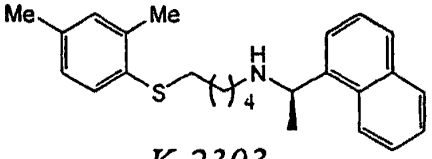
K-2298



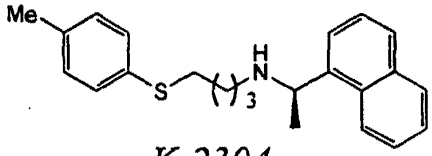
K-2301



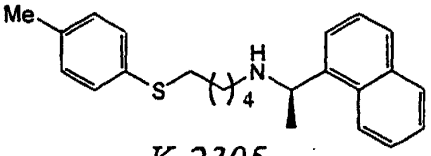
K-2302



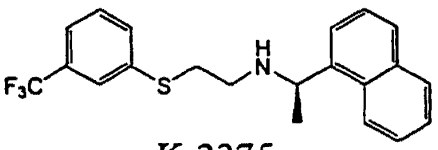
K-2303



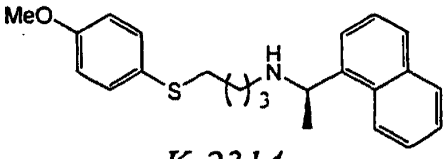
K-2304



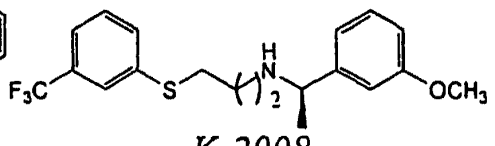
K-2305



K-2275

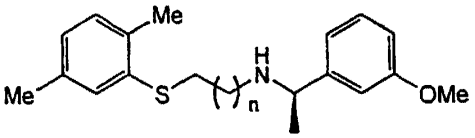


K-2314

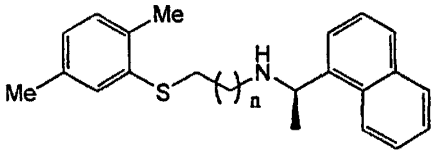


K-2008

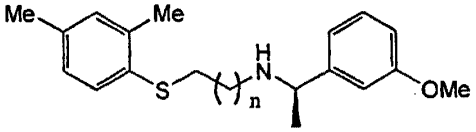
Fig. 27



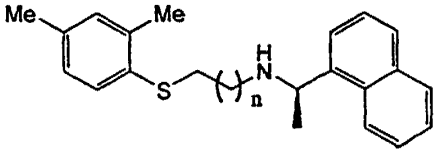
S1: n=1 *S4:* n=4 *S7:* n=7
S2: n=2 *S5:* n=5
S3: n=3 *S6:* n=6



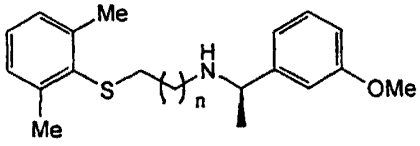
S8: n=1 *S11:* n=4 *S14:* n=7
S9: n=2 *S12:* n=5 *S15:* n=9
S10: n=3 *S13:* n=6 *S16:* n=11



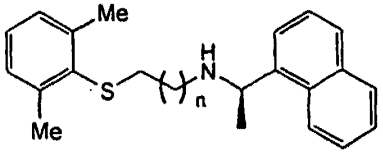
S17: n=1 *S20:* n=4 *S23:* n=7
S18: n=2 *S21:* n=5
S19: n=3 *S22:* n=6



S24: n=1 *S27:* n=6
S25: n=2 *S28:* n=7
S26: n=5

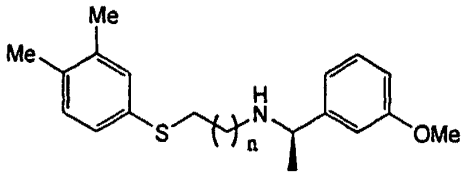


S29: n=1 *S32:* n=4 *S35:* n=7
S30: n=2 *S33:* n=5
S31: n=3 *S34:* n=6

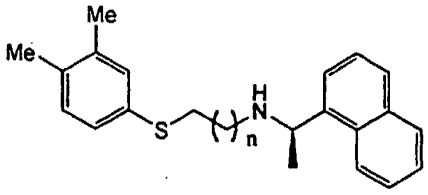


S36: n=1 *S39:* n=4 *S42:* n=7
S37: n=2 *S40:* n=5
S38: n=3 *S41:* n=6

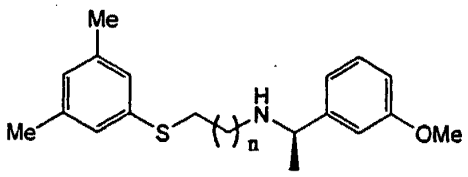
Fig. 28



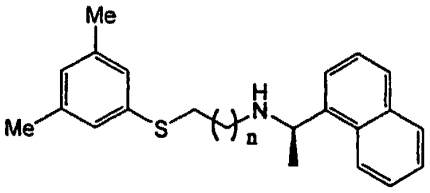
S43: n=1 *S44:* n=2 *S45:* n=3 *S46:* n=4 *S47:* n=5 *S48:* n=6 *S49:* n=7



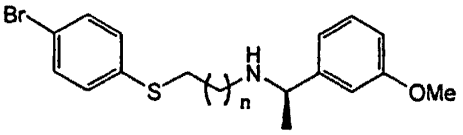
S50: n=1 *S51:* n=2 *S52:* n=3 *S53:* n=4 *S54:* n=5 *S55:* n=6 *S56:* n=7



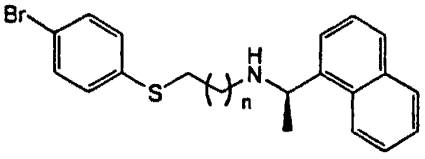
S57: n=1 *S58:* n=2 *S59:* n=3 *S60:* n=4 *S61:* n=5 *S62:* n=6 *S63:* n=7



S64: n=1 *S65:* n=2 *S66:* n=3 *S67:* n=4 *S68:* n=5 *S69:* n=6 *S70:* n=7

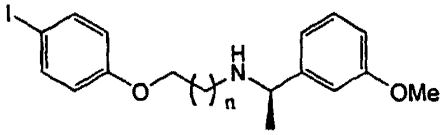


S71: n=1 *S72:* n=2 *S73:* n=3 *S74:* n=4 *S75:* n=5 *S76:* n=6 *S77:* n=7

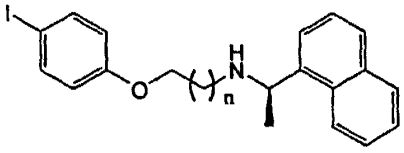


S78: n=1 *S79:* n=2 *S80:* n=3 *S81:* n=4 *S82:* n=5 *S83:* n=6 *S84:* n=7

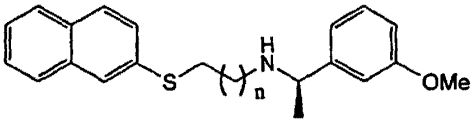
Fig. 29



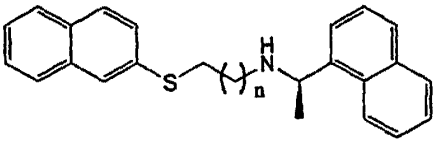
S85: n=2 *S88:* n=5
S86: n=3 *S89:* n=6
S87: n=4 *S90:* n=7



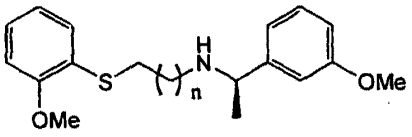
S91: n=2 *S94:* n=5
S92: n=3 *S95:* n=6
S93: n=4 *S96:* n=7



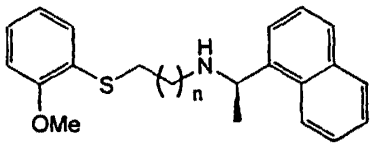
S97: n=1 *S100:* n=4 *S103:* n=7
S98: n=2 *S101:* n=5
S99: n=3 *S102:* n=6



S104: n=1 *S107:* n=4 *S110:* n=7
S105: n=2 *S108:* n=5
S106: n=3 *S109:* n=6

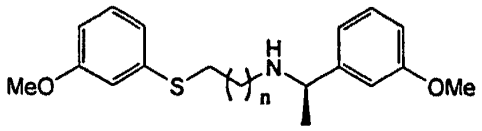


S111: n=1 *S114:* n=4 *S117:* n=7
S112: n=2 *S115:* n=5
S113: n=3 *S116:* n=6

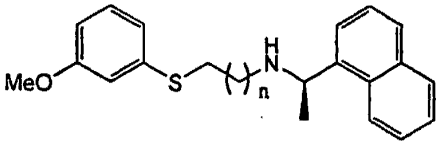


S118: n=1 *S121:* n=4 *S124:* n=7
S119: n=2 *S122:* n=5
S120: n=3 *S123:* n=6

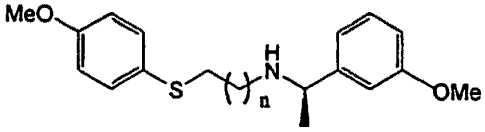
Fig. 30



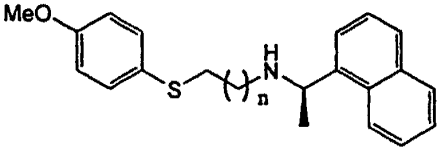
S125: n=1 *S128:* n=4 *S131:* n=7
S126: n=2 *S129:* n=5
S127: n=3 *S130:* n=6



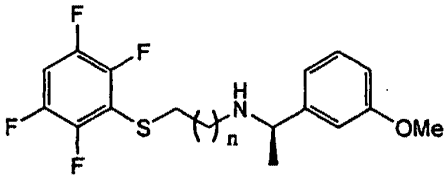
S132: n=1 *S135:* n=4 *S138:* n=7
S133: n=2 *S136:* n=5
S134: n=3 *S137:* n=6



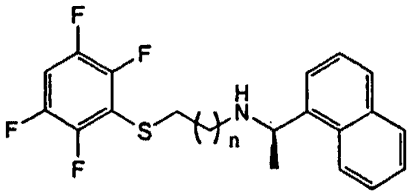
S139: n=1 *S142:* n=4 *S145:* n=7
S140: n=2 *S143:* n=5
S141: n=3 *S144:* n=6



S146: n=1 *S149:* n=4 *S152:* n=7
S147: n=2 *S150:* n=5
S148: n=3 *S151:* n=6

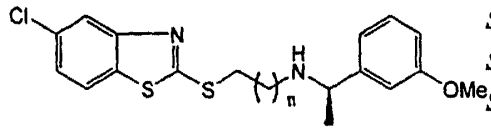


S153: n=1 *S156:* n=4 *S159:* n=7
S154: n=2 *S157:* n=5
S155: n=3 *S158:* n=6

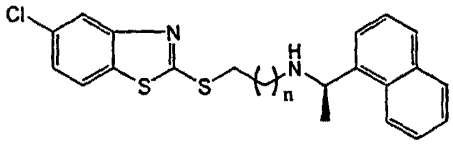


S160: n=1 *S163:* n=4 *S166:* n=7
S161: n=2 *S164:* n=5
S162: n=3 *S165:* n=6

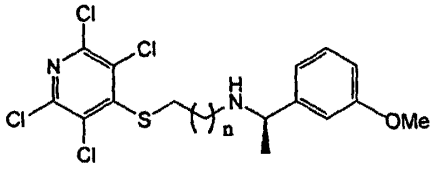
Fig. 31



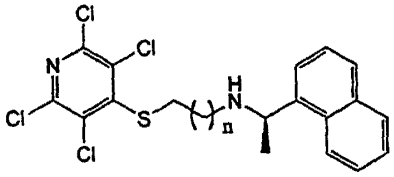
S167: n=1 *S170:* n=4 *S173:* n=7
S168: n=2 *S171:* n=5
S169: n=3 *S172:* n=6



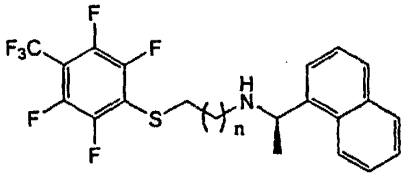
S174: n=1 *S177:* n=4 *S180:* n=7
S175: n=2 *S178:* n=5
S176: n=3 *S179:* n=6



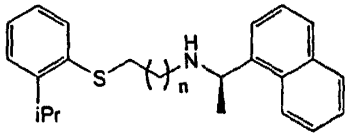
S181: n=1 *S184:* n=4 *S187:* n=7
S182: n=2 *S185:* n=5
S183: n=3 *S186:* n=6



S188: n=1 *S191:* n=4 *S194:* n=7
S189: n=2 *S192:* n=5
S190: n=3 *S193:* n=6

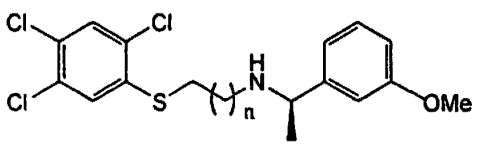


S195: n=1 *S198:* n=6 *S201:* n=11
S196: n=2 *S199:* n=7
S197: n=5 *S200:* n=9

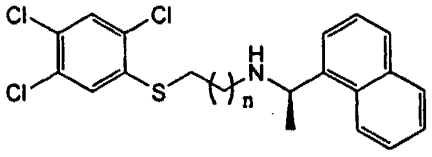


S202: n=1 *S205:* n=4 *S208:* n=7
S203: n=2 *S206:* n=5
S204: n=3 *S207:* n=6

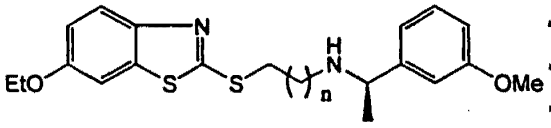
Fig. 32



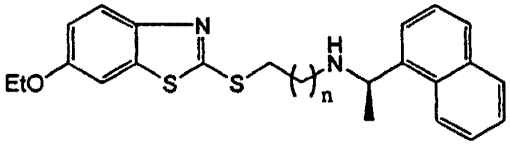
S209: n=1 *S212:* n=4 *S215:* n=7
S210: n=2 *S213:* n=5
S211: n=3 *S214:* n=6



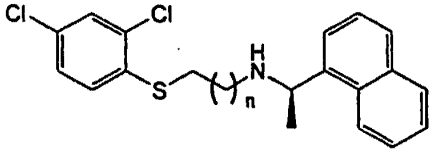
S216: n=2 *S219:* n=7
S217: n=5
S218: n=6



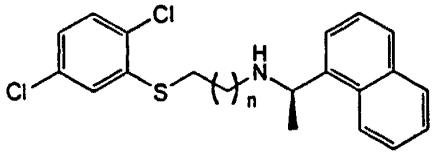
S220: n=2 *S223:* n=5
S221: n=3 *S224:* n=6
S222: n=4 *S225:* n=7



S226: n=1 *S229:* n=4 *S232:* n=7
S227: n=2 *S230:* n=5
S228: n=3 *S231:* n=6

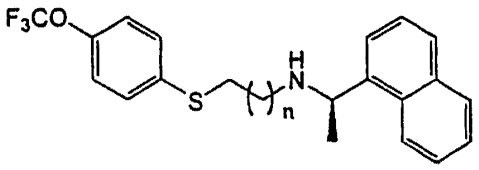


S233: n=1 *S236:* n=4
S234: n=2
S235: n=3

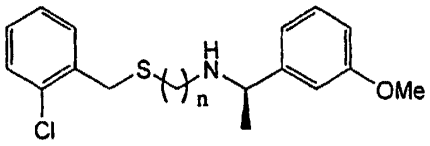


S237: n=2 *S240:* n=7
S238: n=5
S239: n=6

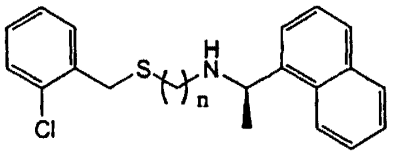
Fig. 33



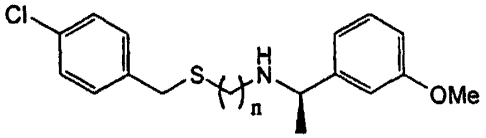
S241: n=1 *S244:* n=7
S242: n=2
S243: n=6



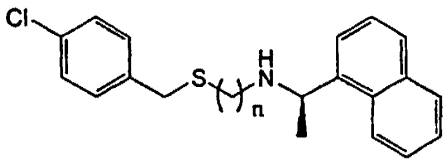
S245: n=2 *S248:* n=6
S246: n=3
S247: n=5



S249: n=2
S250: n=3



S251: n=2
S252: n=3



S253: n=2
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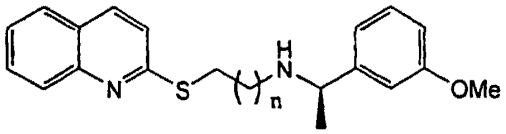
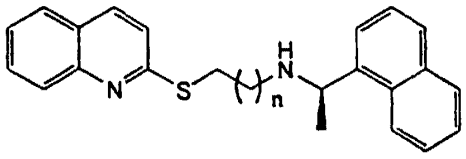


S255: n=3
S256: n=4
S257: n=5



S258: n=3
S259: n=4
S260: n=5

Fig. 34

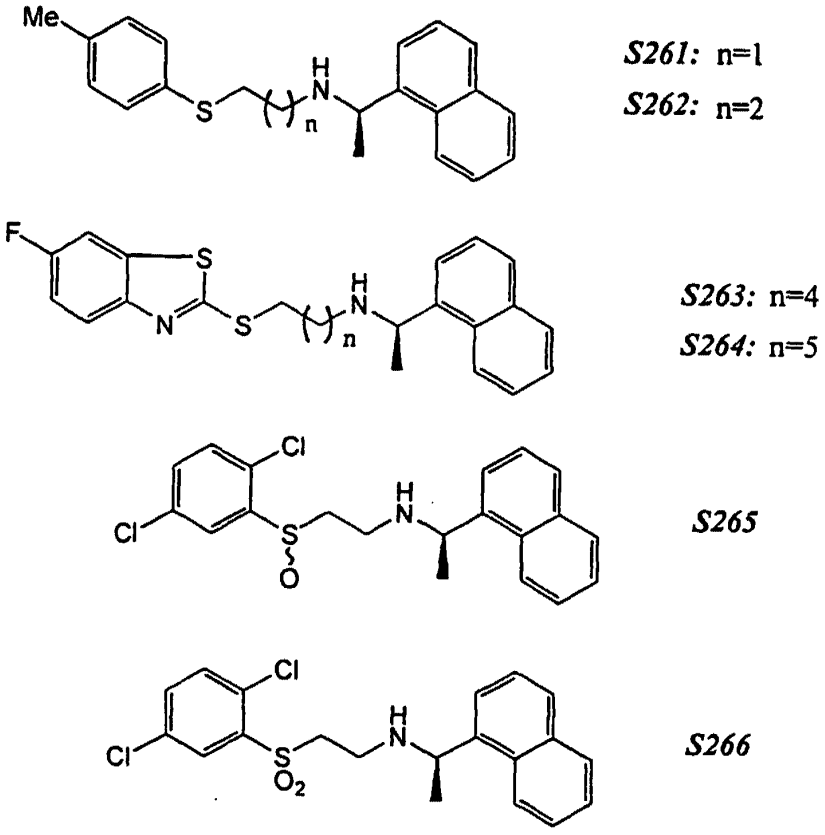
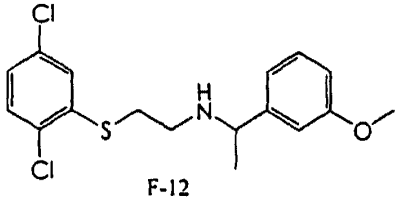

Me
S
H
N
n
S261: n=1
S262: n=2
F
S
N
S
H
N
n
S263: n=4
S264: n=5
Cl
Cl
S
O
H
N
S265
Cl
Cl
S
O2
H
N
S266

Fig. 35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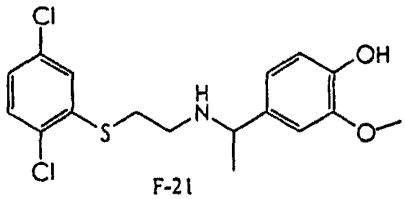
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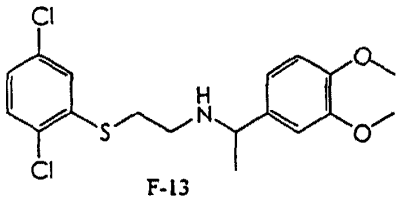
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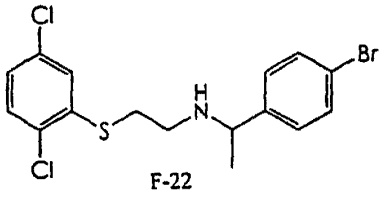
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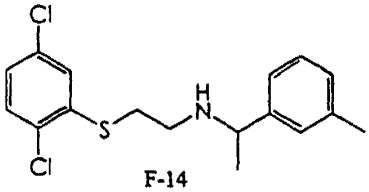
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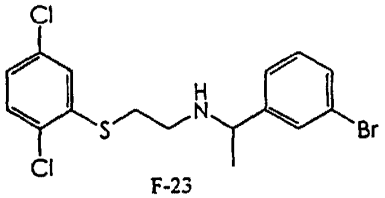
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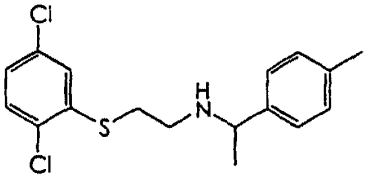
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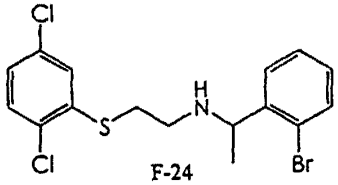
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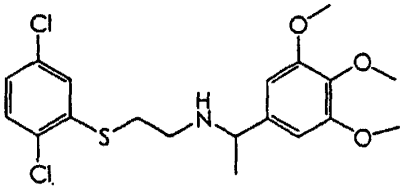
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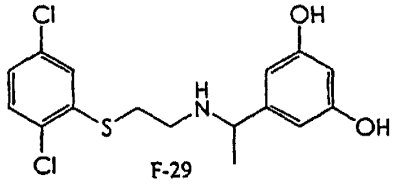
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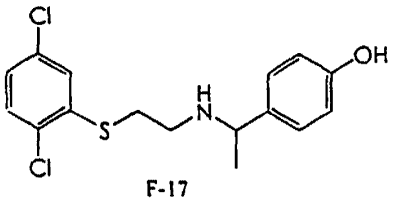
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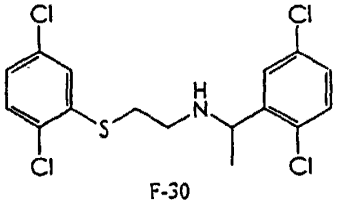
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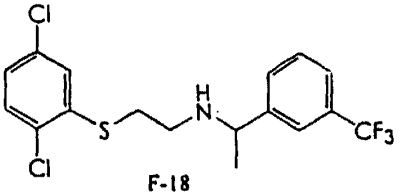
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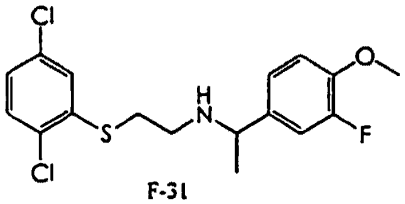
Fig. 36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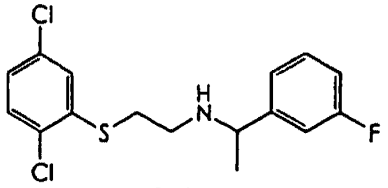
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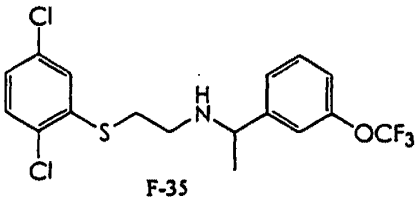
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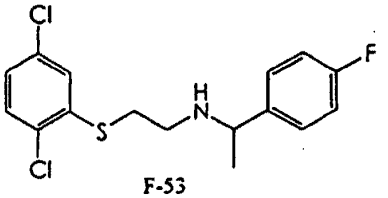
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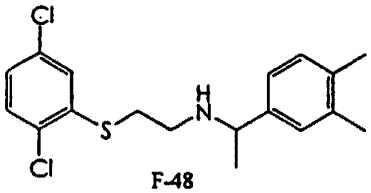
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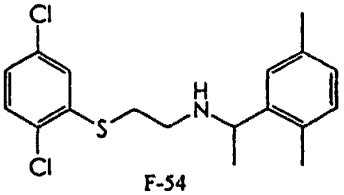
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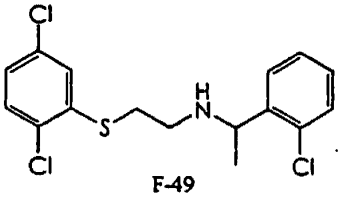
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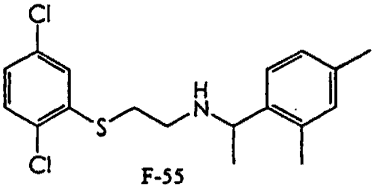
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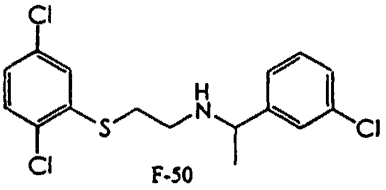
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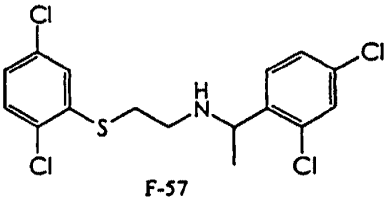
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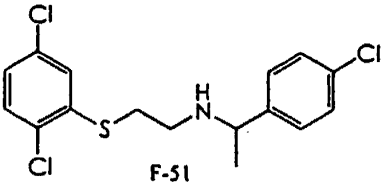
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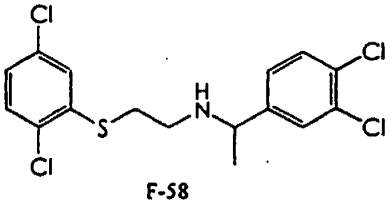
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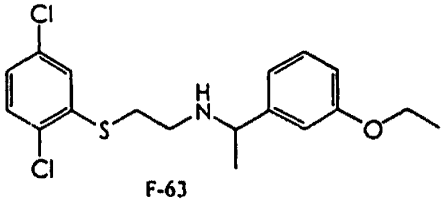
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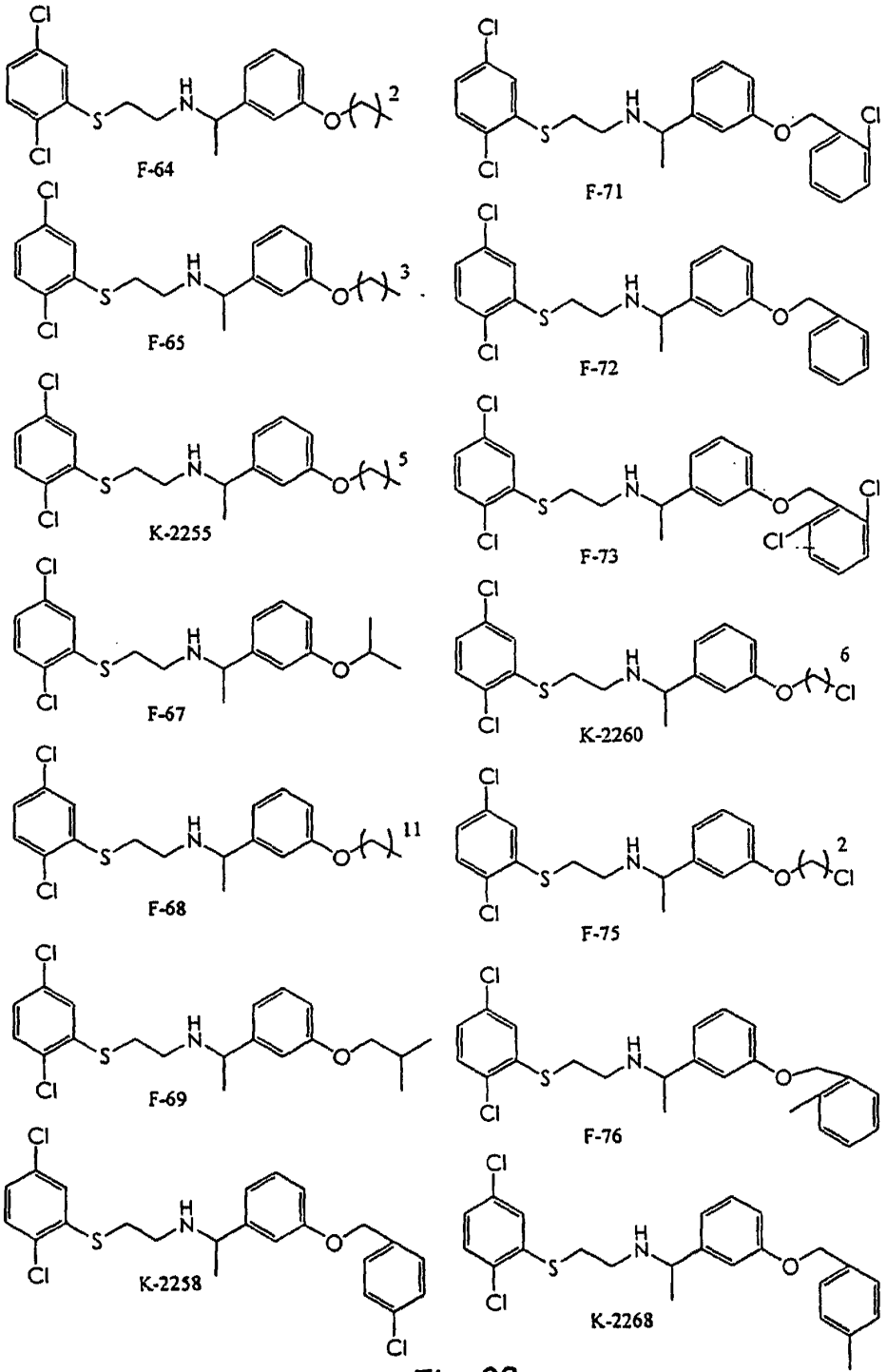
Fig. 37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F-65
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F-67
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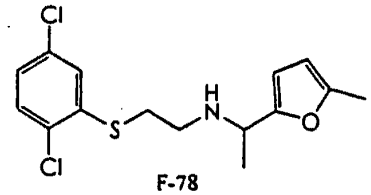
K-2268

Fig. 38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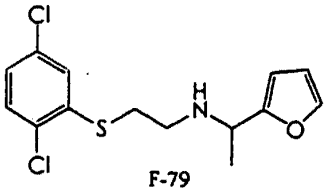
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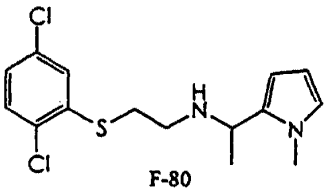
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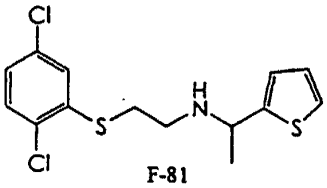
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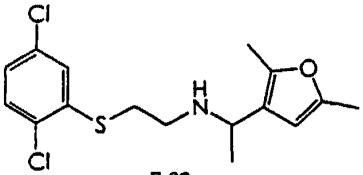
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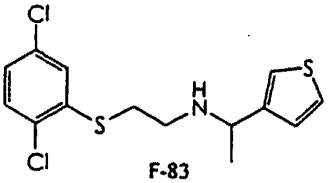
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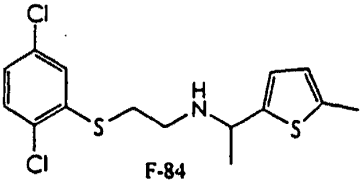
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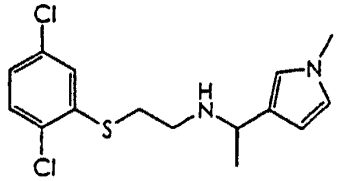
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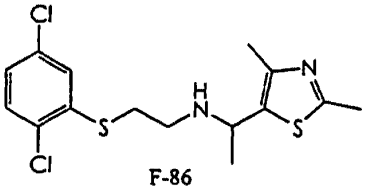
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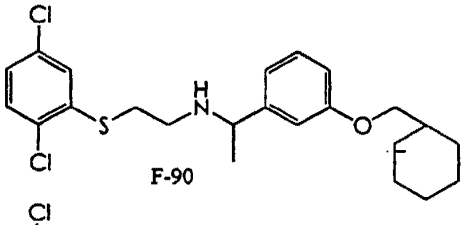
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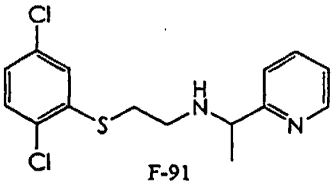
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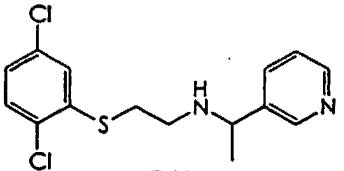
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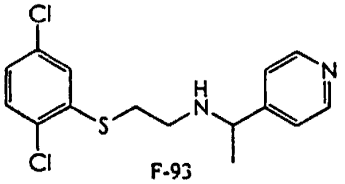
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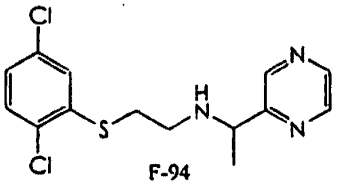

F-94

Fig. 39

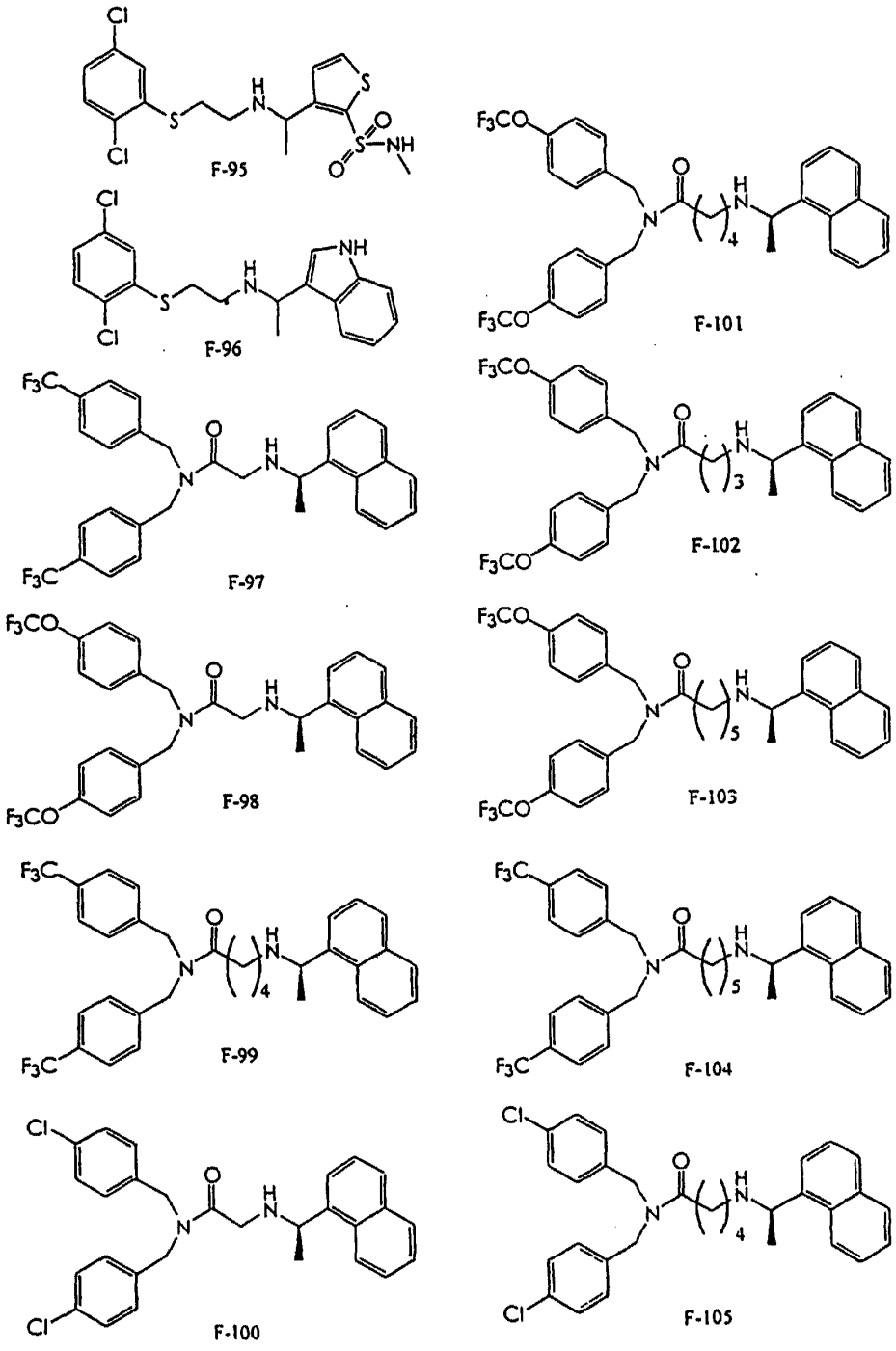


Fig. 40

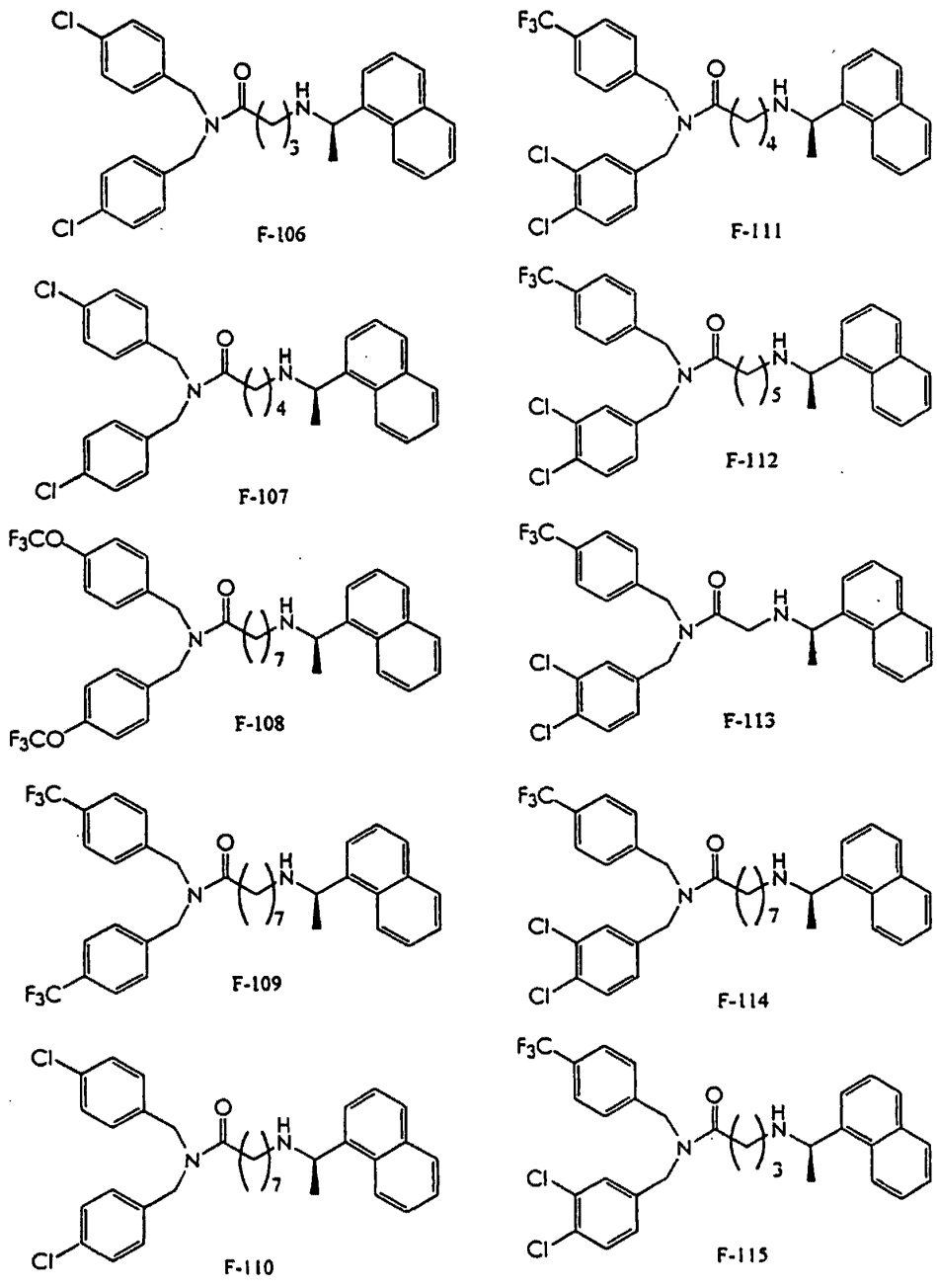
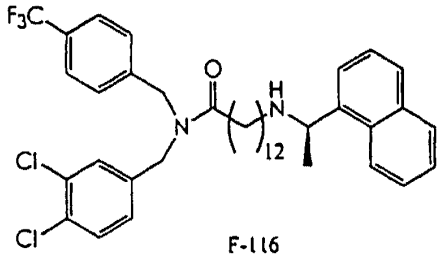


Fig. 41



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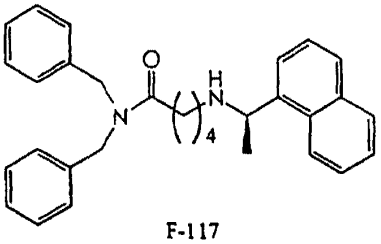
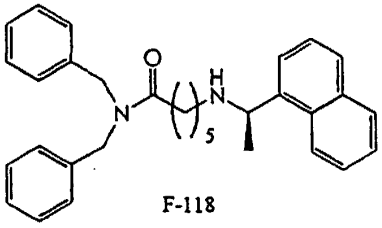
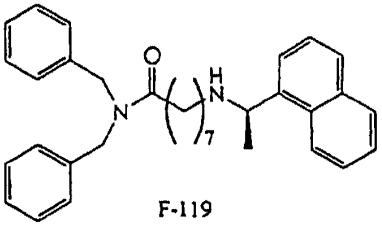


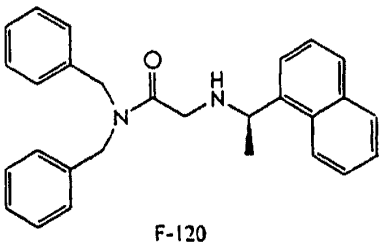
F-117



F-118

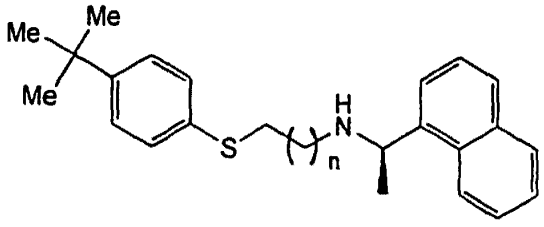


F-119

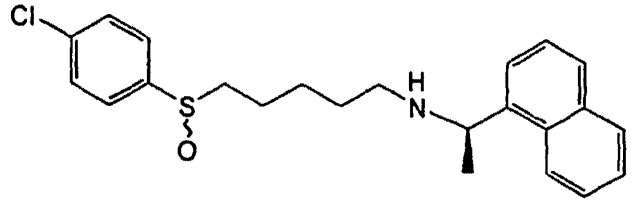


F-120

Fig. 42



S267: n=1 *S271:* n=5
S268: n=2 *S272:* n=6
S269: n=3 *S273:* n=7
S270: n=4



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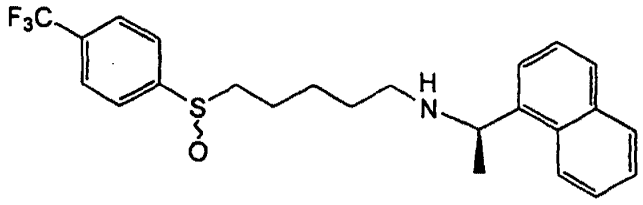
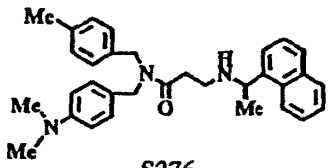


S275

Fig. 43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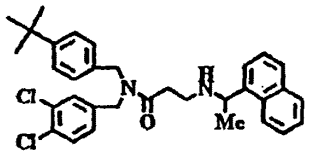
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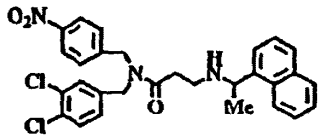
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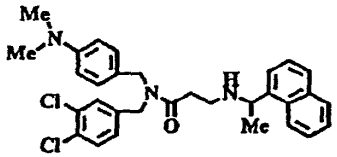
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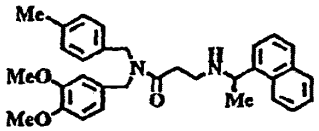
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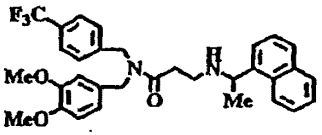
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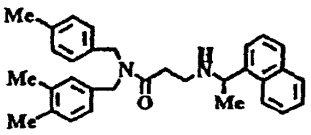
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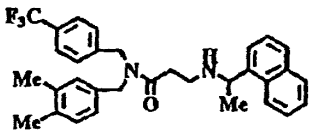
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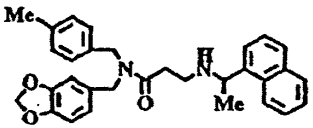
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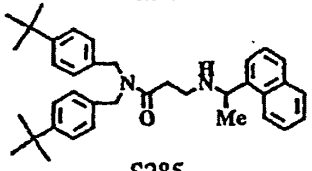
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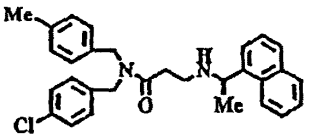
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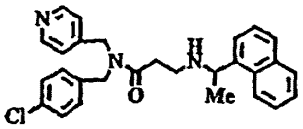
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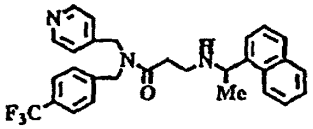
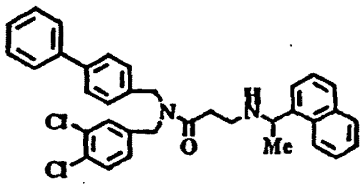

S288

Fig. 44



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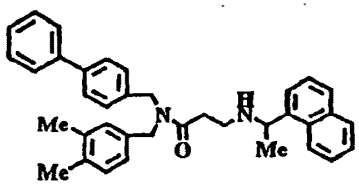

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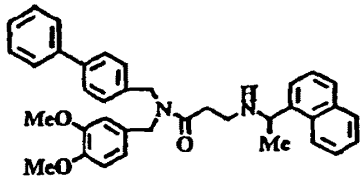

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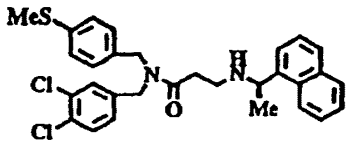

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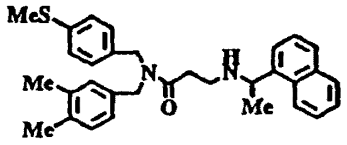

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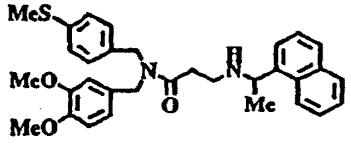
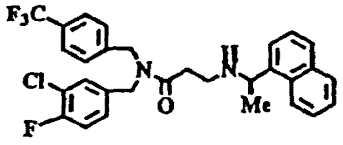


S294



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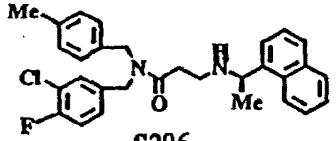

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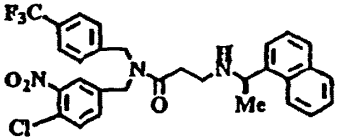

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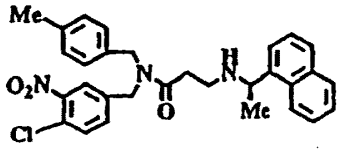

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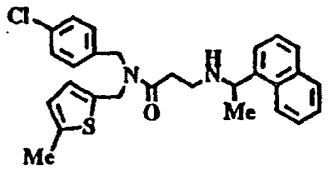
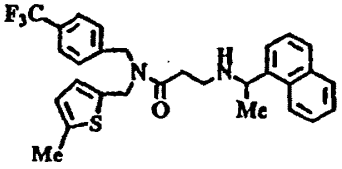


S299



S300

Fig. 45

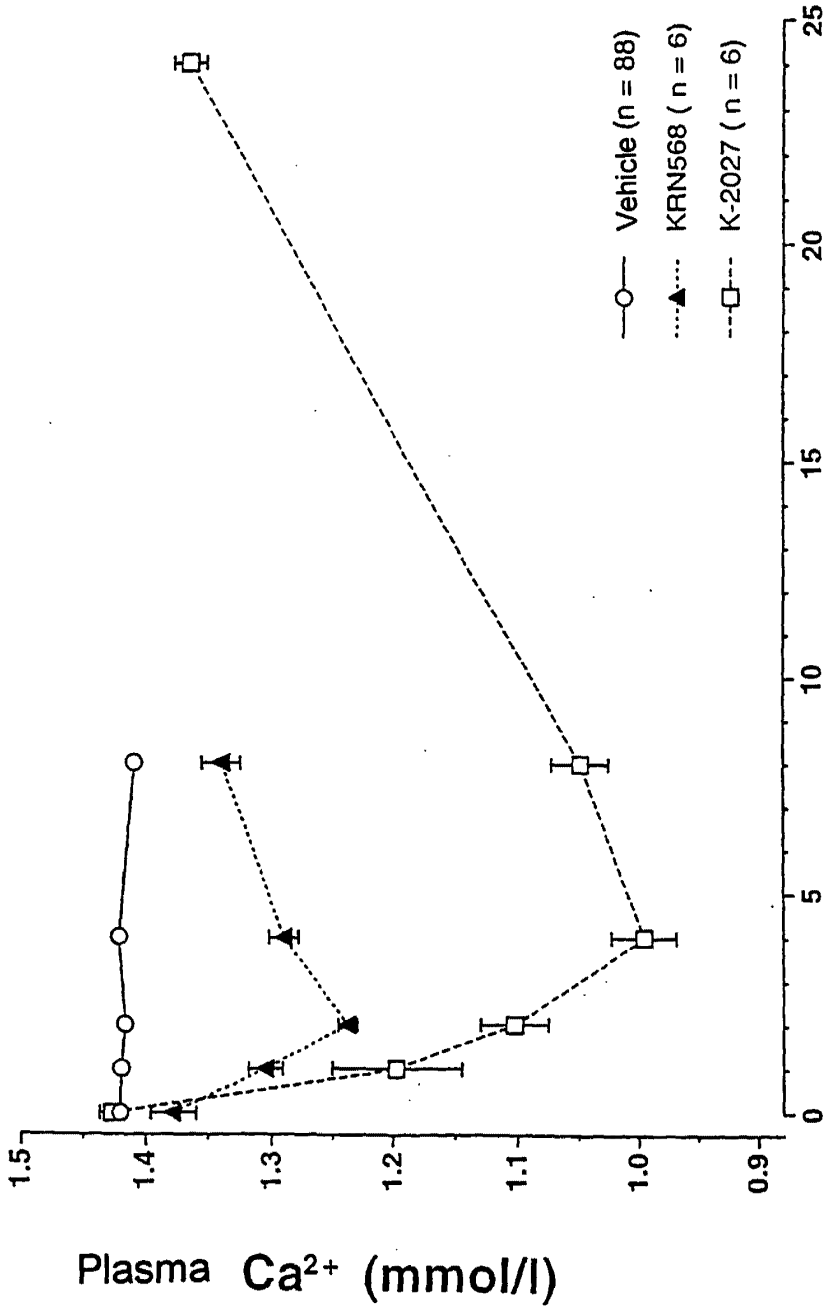

Vehicle (n = 88)
KRN568 (n = 6)
K-2027 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
Time (hr)

Fig. 46

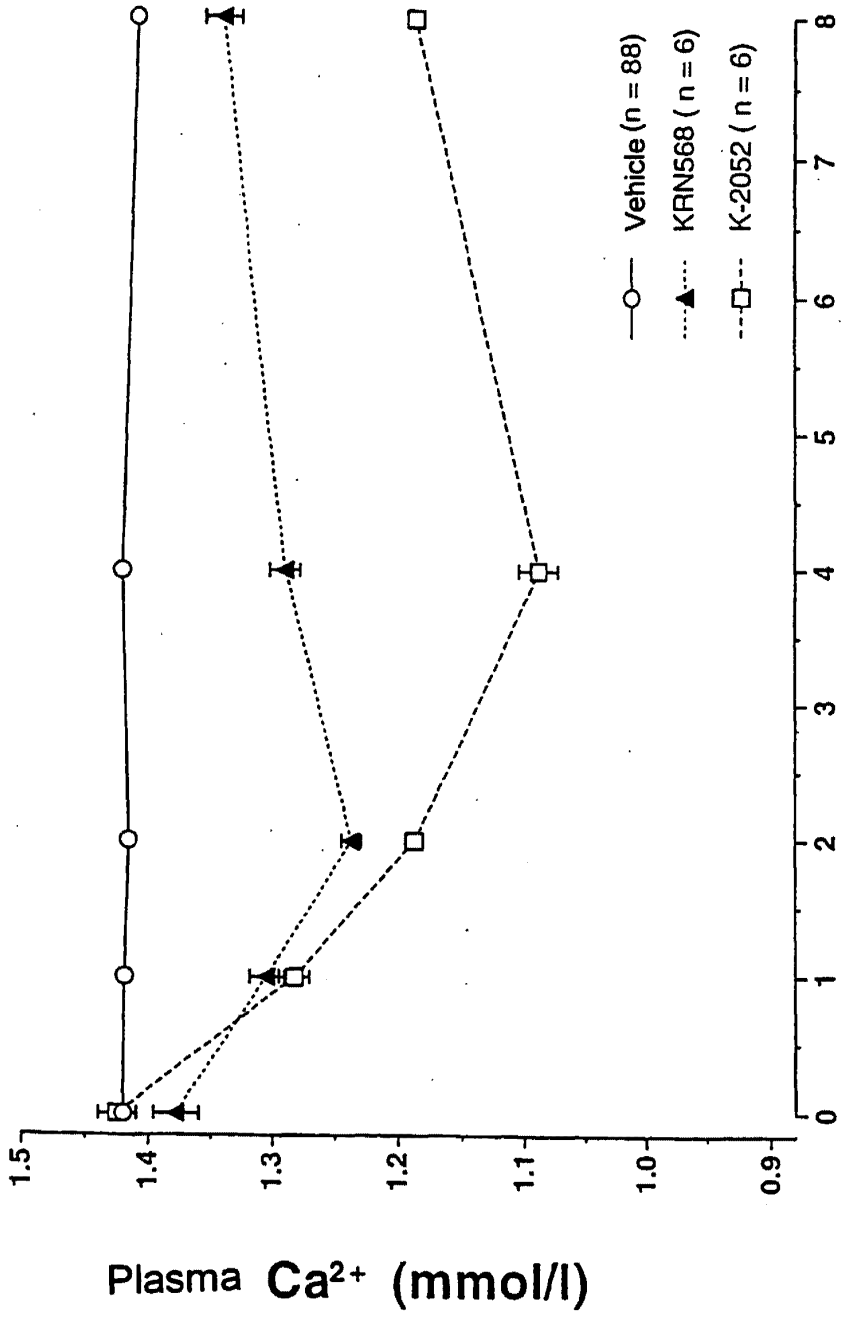

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2052 (n = 6)

Fig. 47

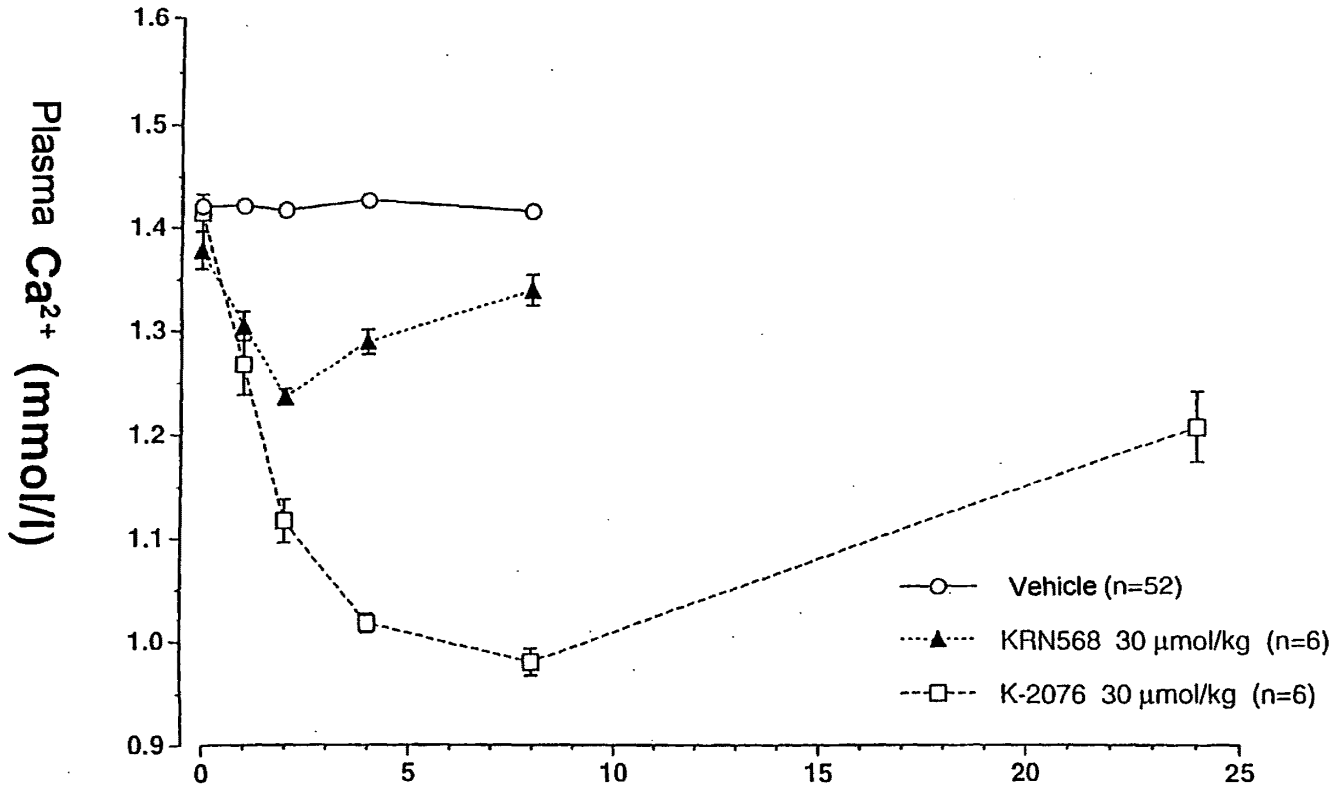

Plasma Ca2+ (mmol/l)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
Time (hr)
Vehicle (n=52)
KRN568 30 µmol/kg (n=6)
K-2076 30 µmol/kg (n=6)

Fig. 48

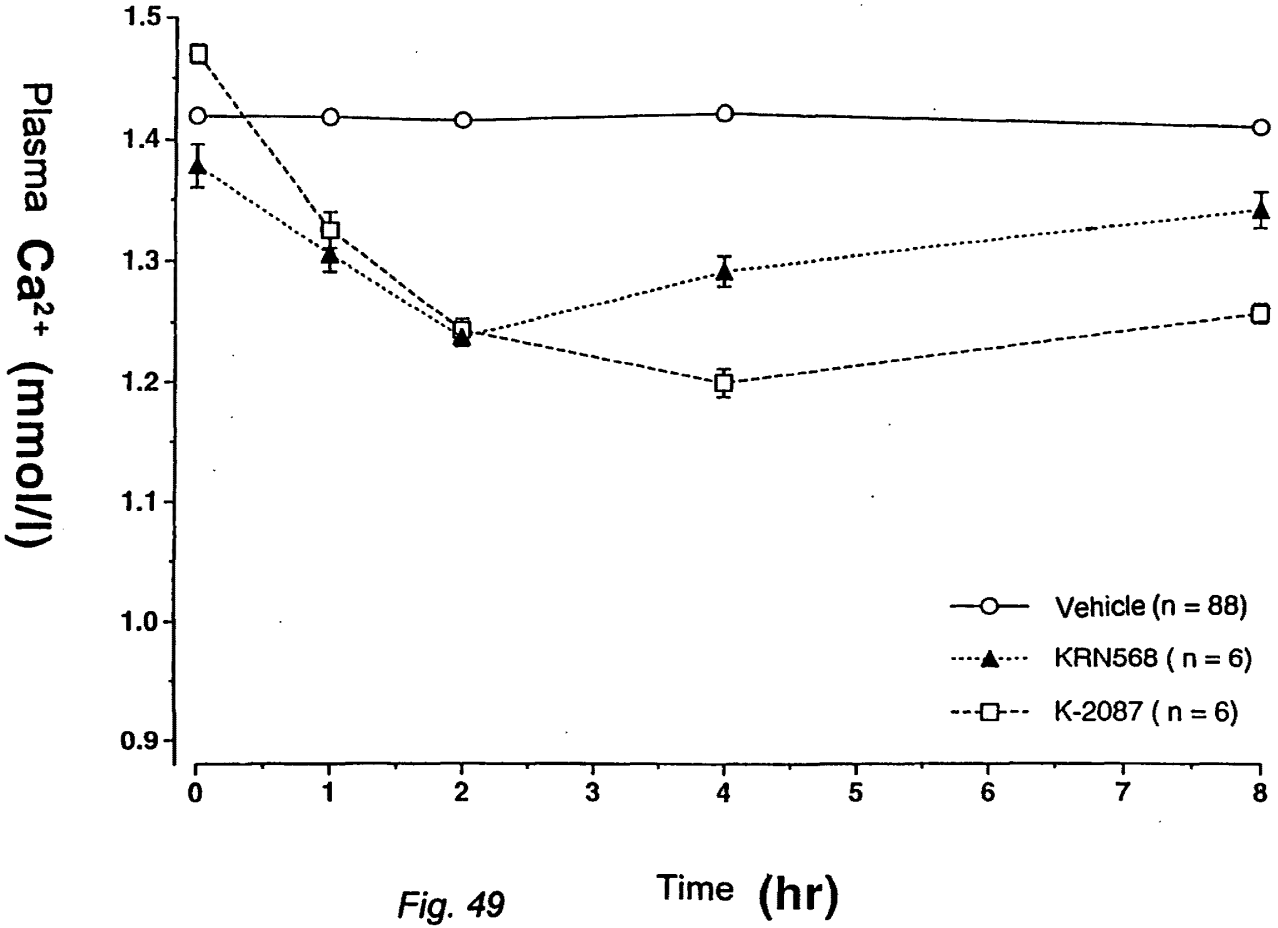

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2087 (n = 6)

Fig. 49

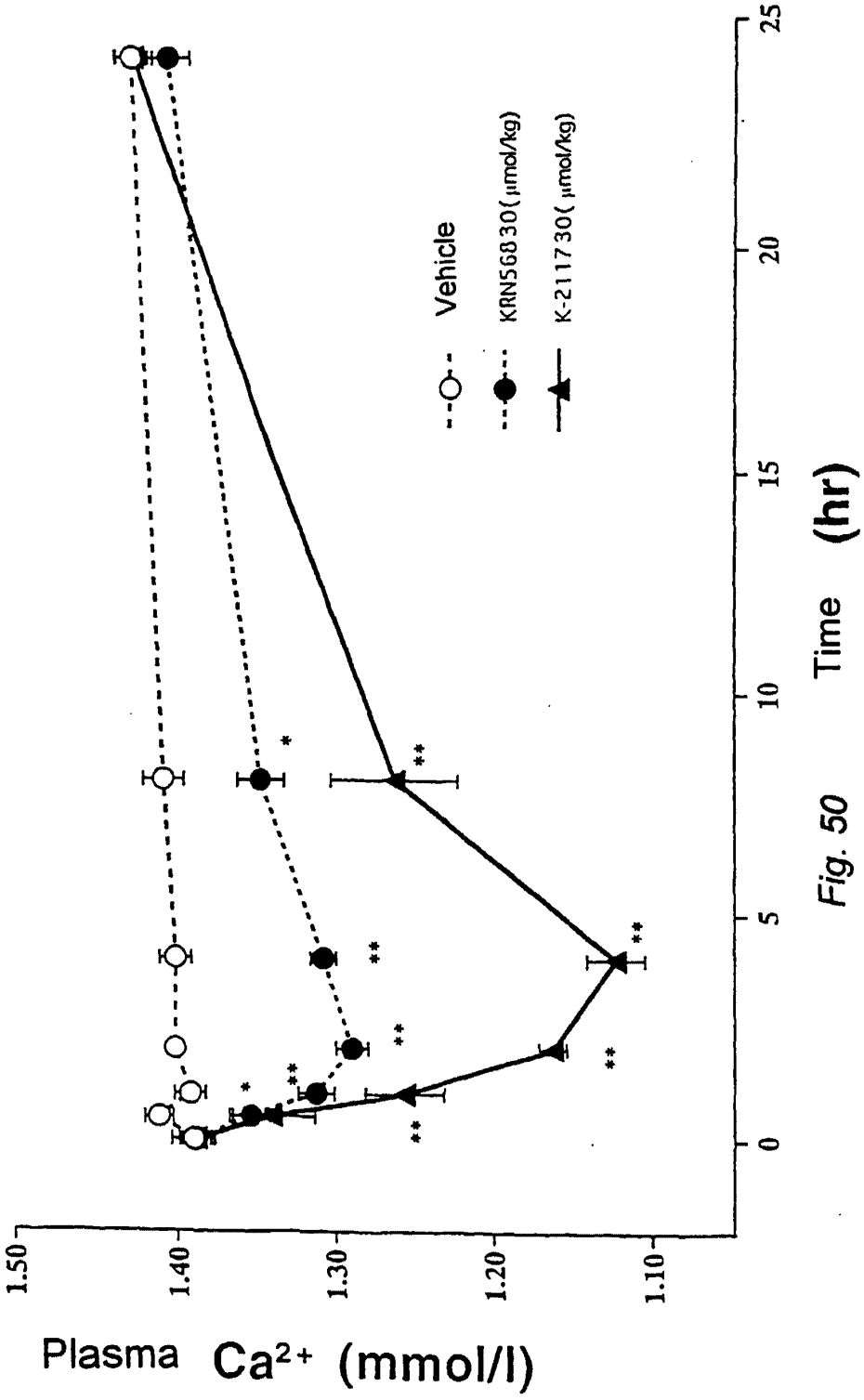

Plasma Ca2+ (mmol/l)
1.50
1.40
1.30
1.20
1.10
0
5
10
15
20
25
Time (hr)
Vehicle
KRN5683O(μmol/kg)
K-211730(μmol/kg)

Fig. 50

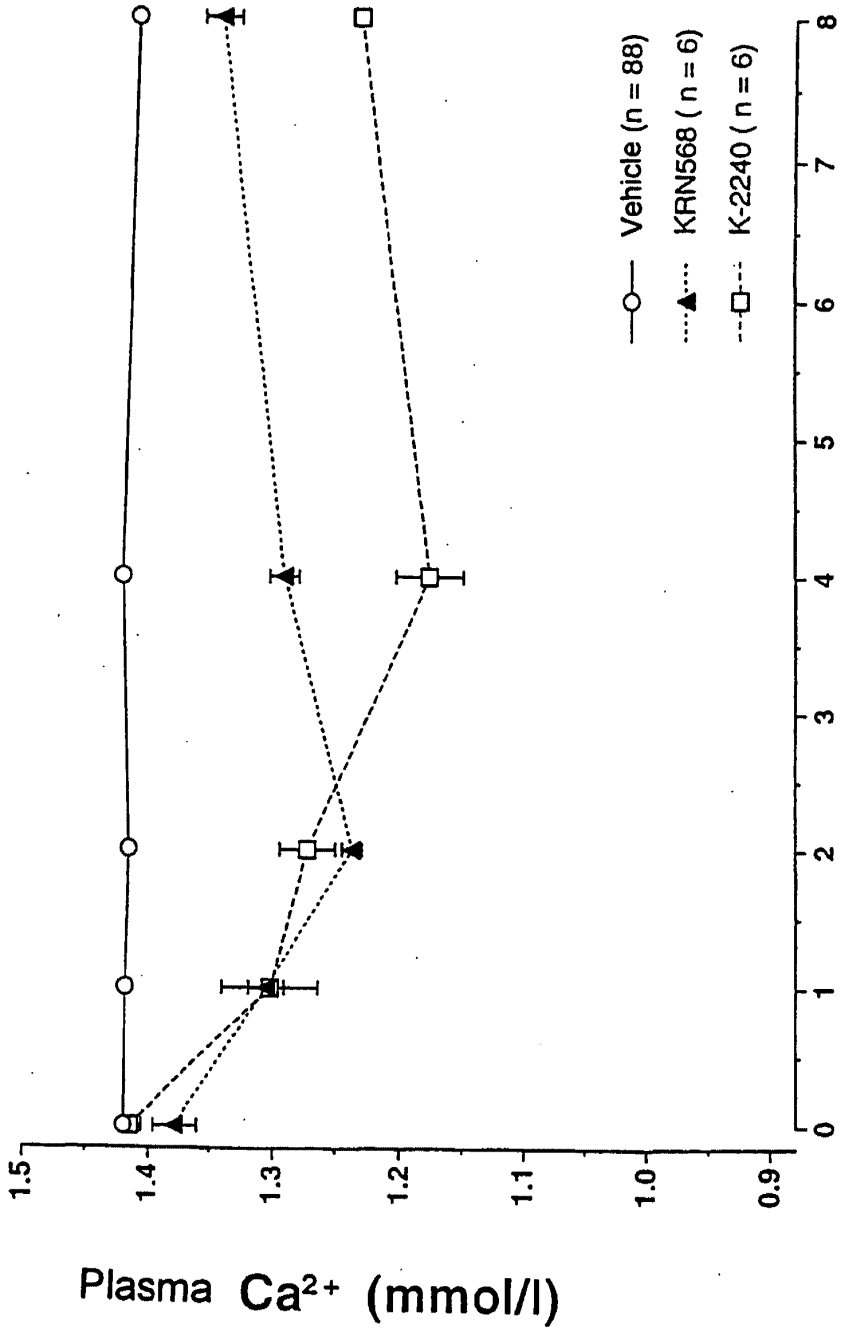

Vehicle (n = 88)
KRN568 (n = 6)
K-2240 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)

Fig. 51

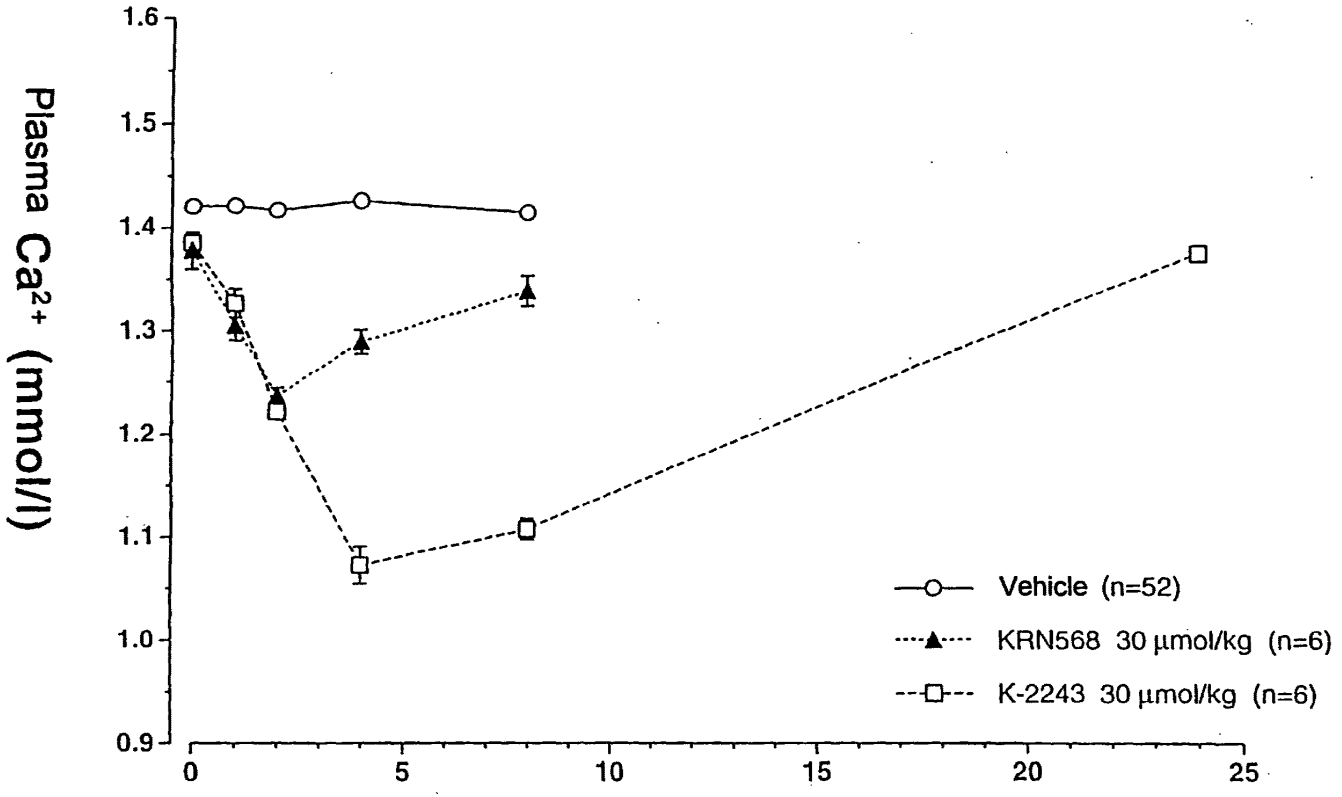

Plasma Ca2+ (mmol/l)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
Time (hr)
Vehicle (n=52)
KRN568 30 µmol/kg (n=6)
K-2243 30 µmol/kg (n=6)

Fig. 52

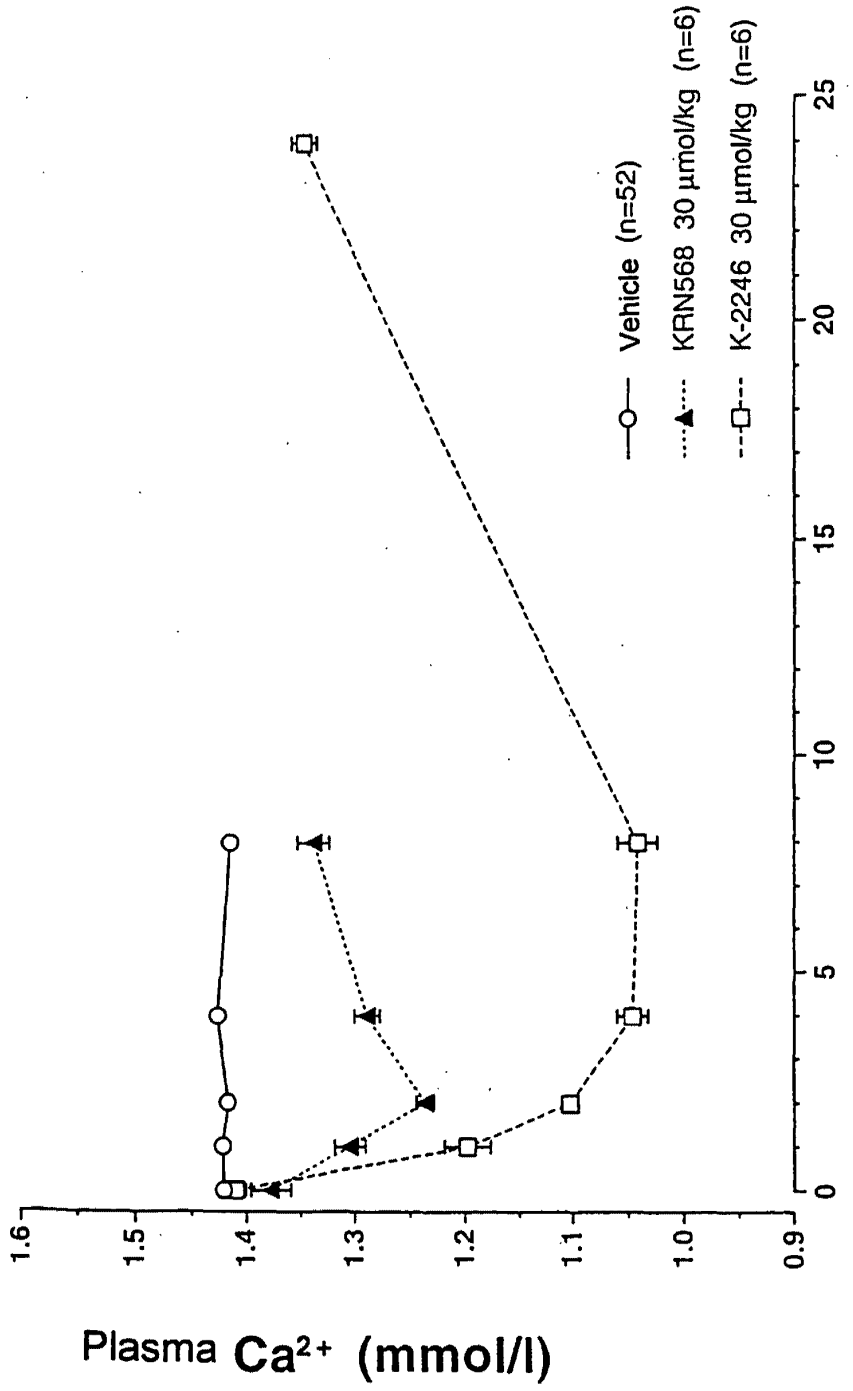

Vehicle (n=52)
KRN568 30 µmol/kg (n=6)
K-2246 30 µmol/kg (n=6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25

Fig. 53

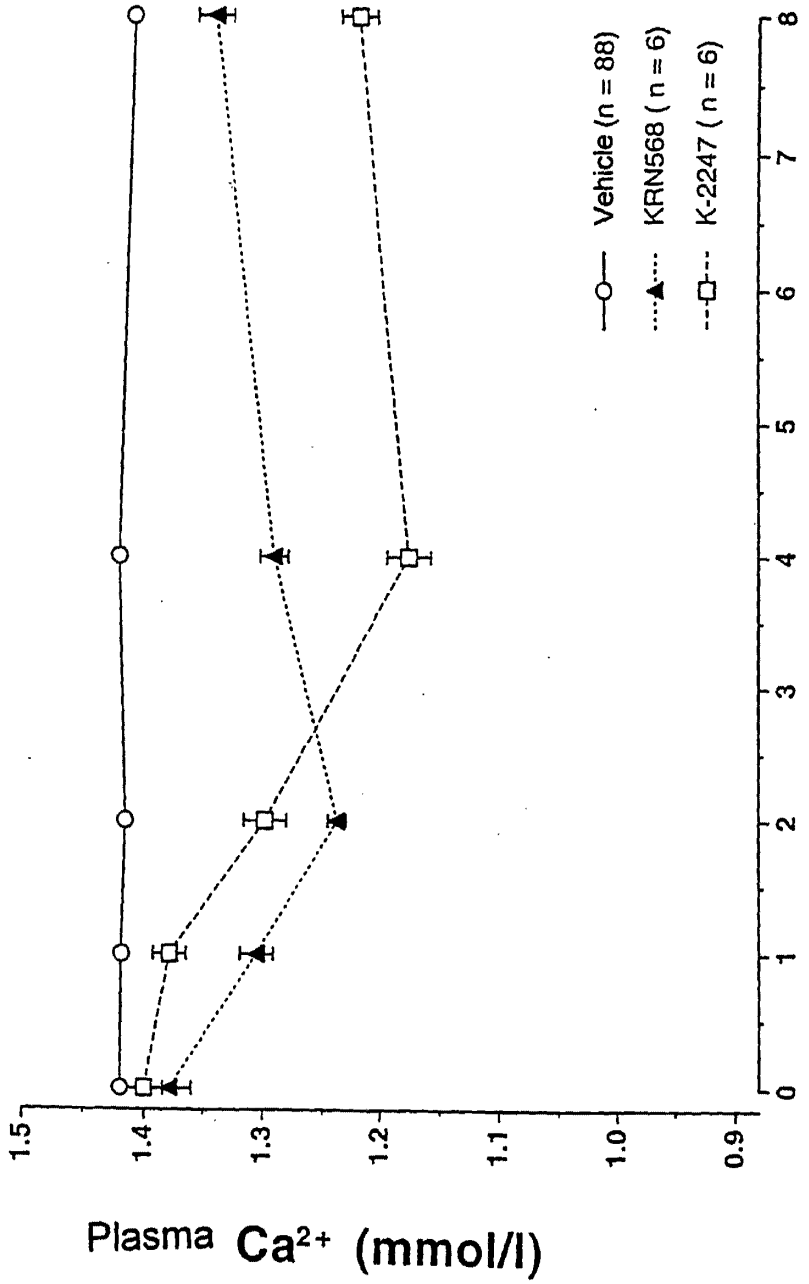

Vehicle (n = 88)
KRN568 (n = 6)
K-2247 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)

Fig. 54

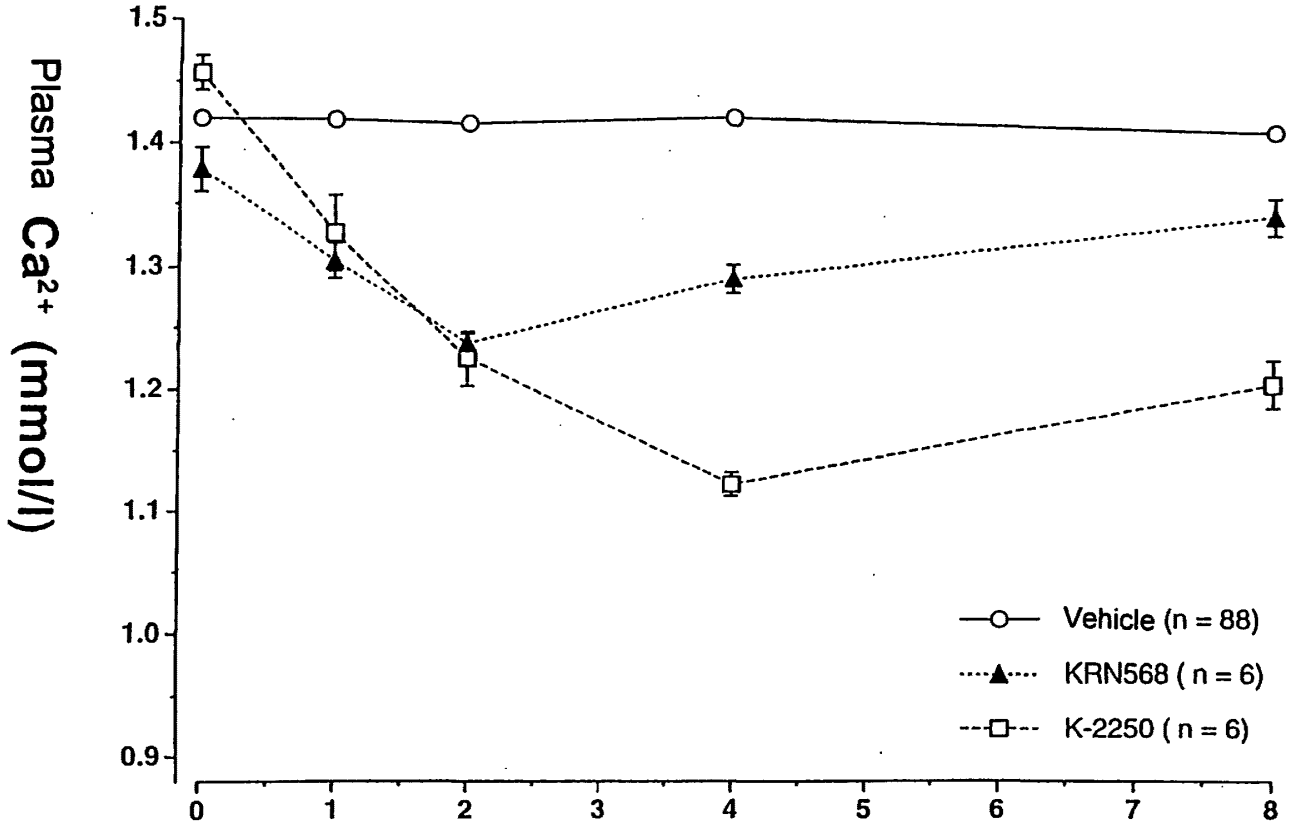
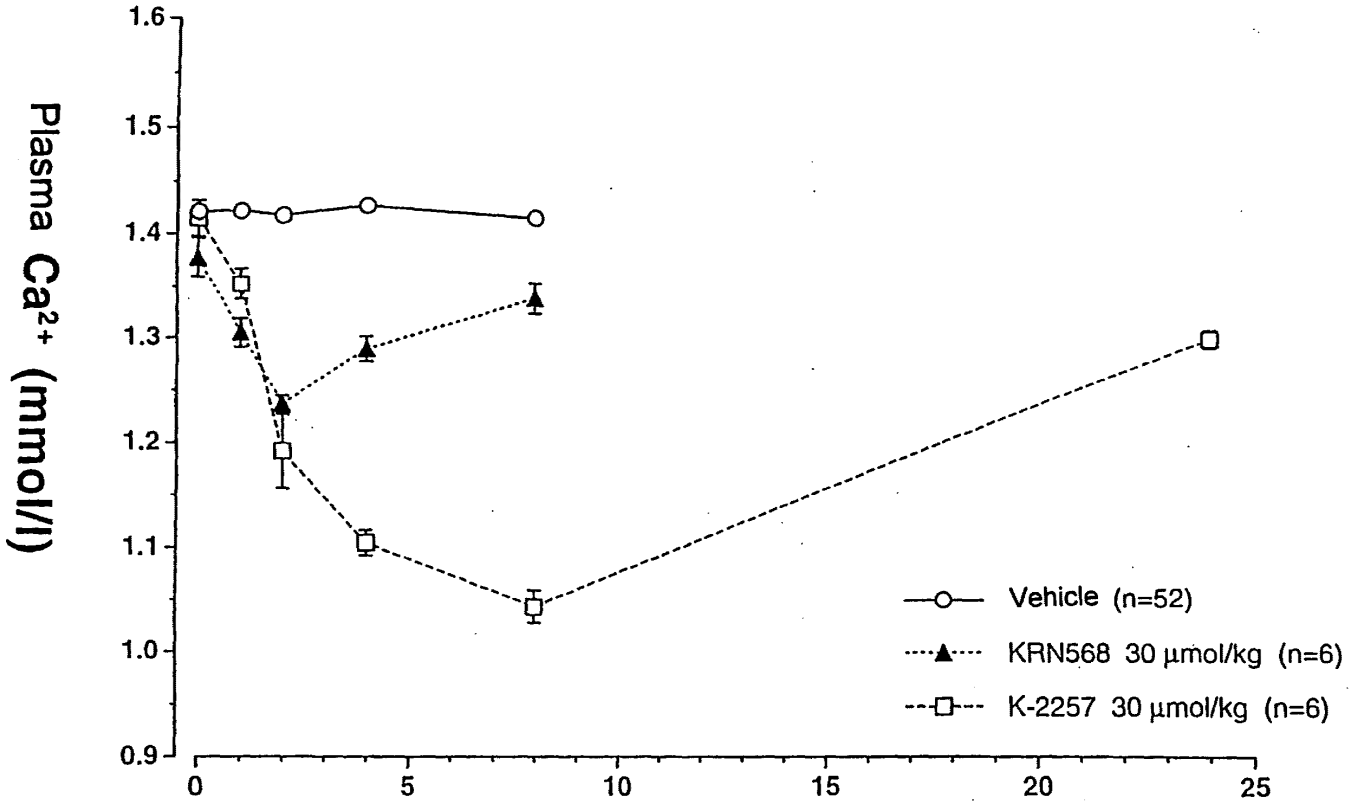

Plasma Ca^{2+} (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2250 (n = 6)

Fig. 55


Plasma Ca2+ (mmol/l)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
Time (hr)
Vehicle (n=52)
KRN568 30 µmol/kg (n=6)
K-2257 30 µmol/kg (n=6)

202

Fig. 56

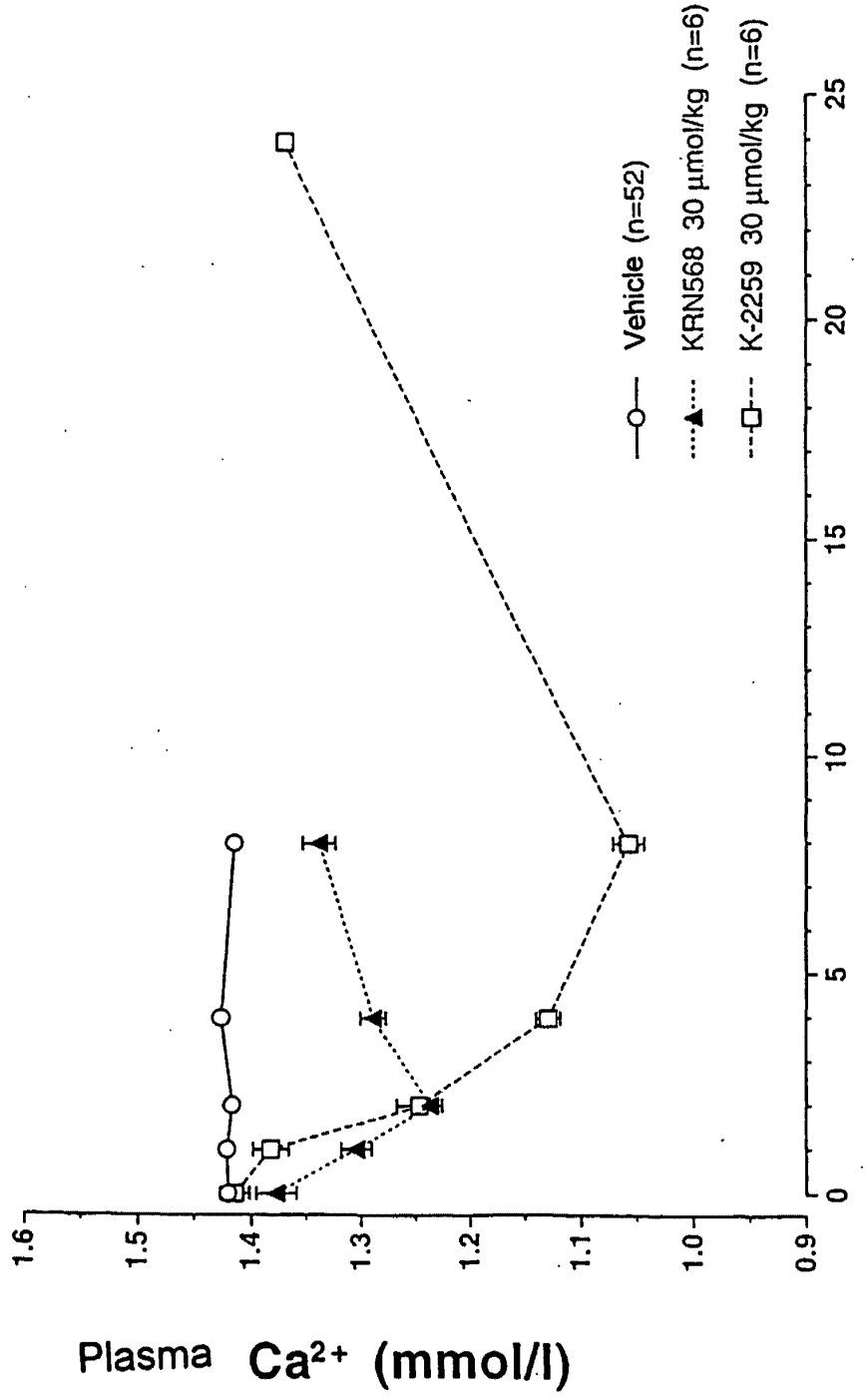

Vehicle (n=52)
KRN568 30 µmol/kg (n=6)
K-2259 30 µmol/kg (n=6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25

Fig. 57

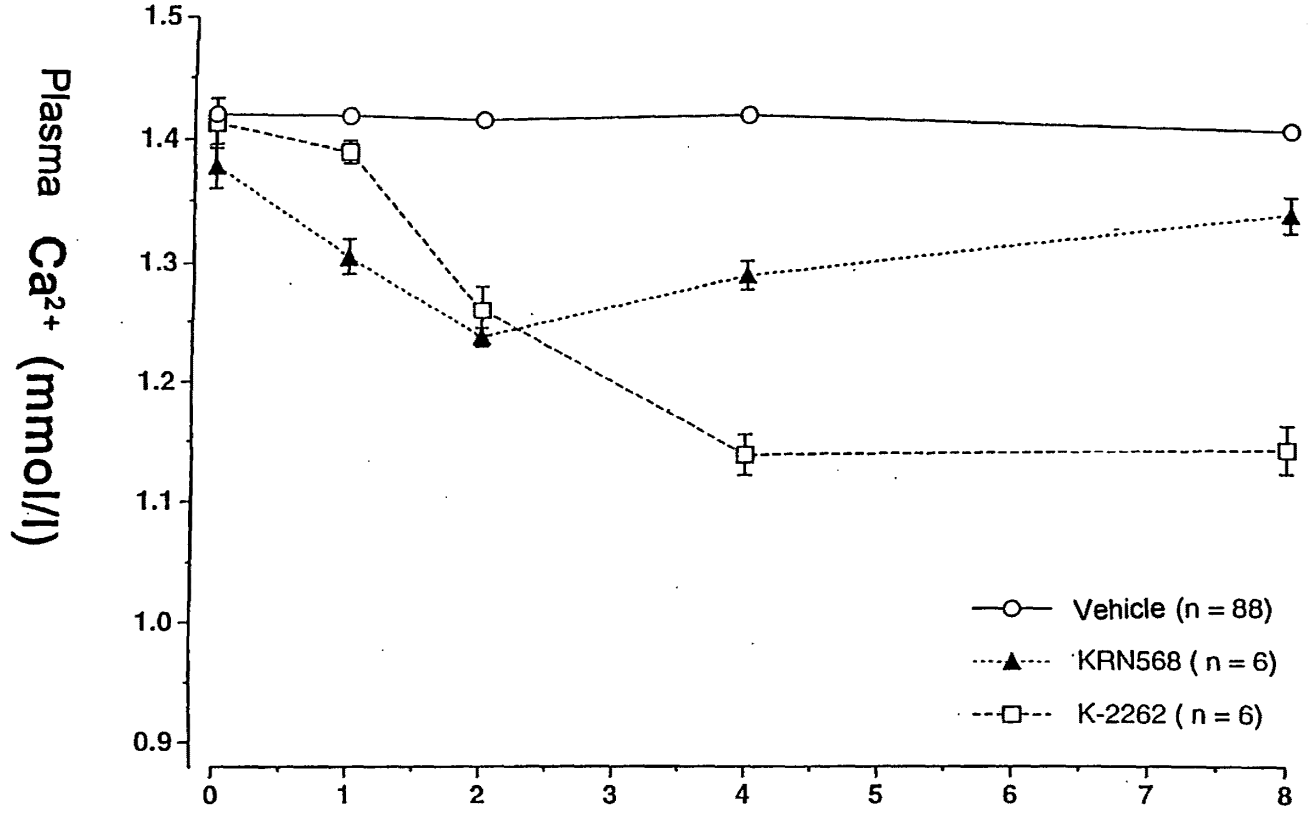

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2262 (n = 6)

Fig. 58

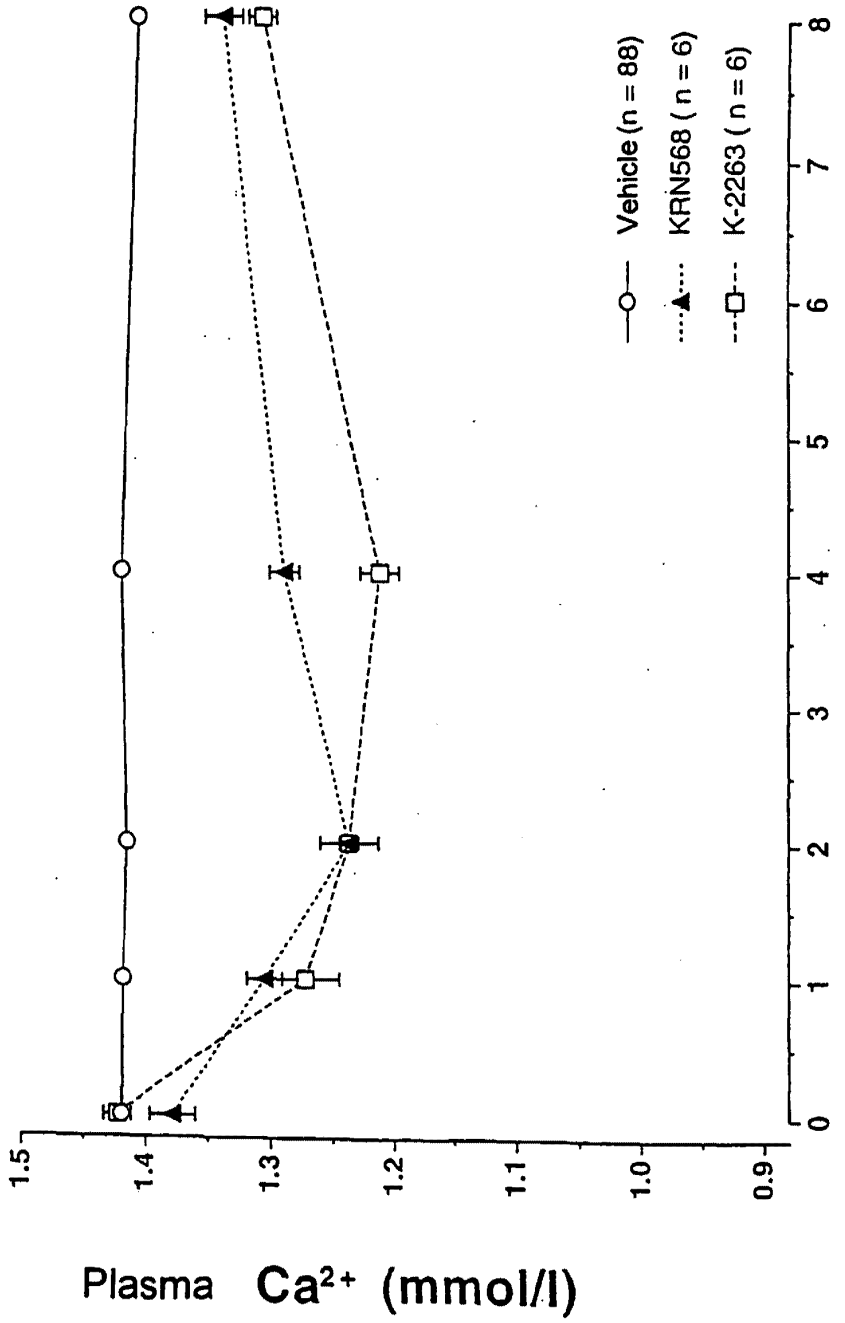

Vehicle (n = 88)
KRN568 (n = 6)
K-2263 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)

Fig. 59

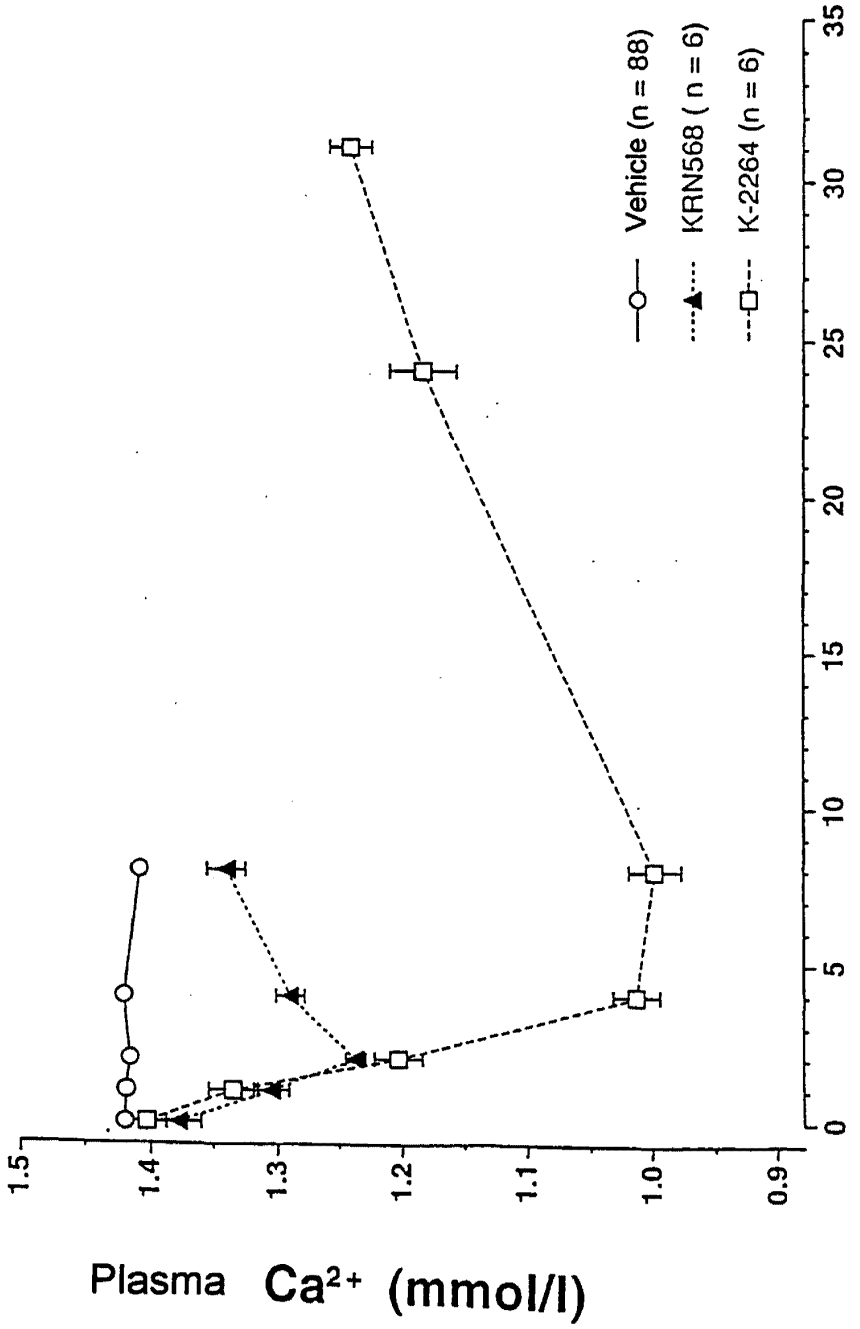

Vehicle (n = 88)
KRN568 (n = 6)
K-2264 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30
35
Time (hr)

Fig. 60

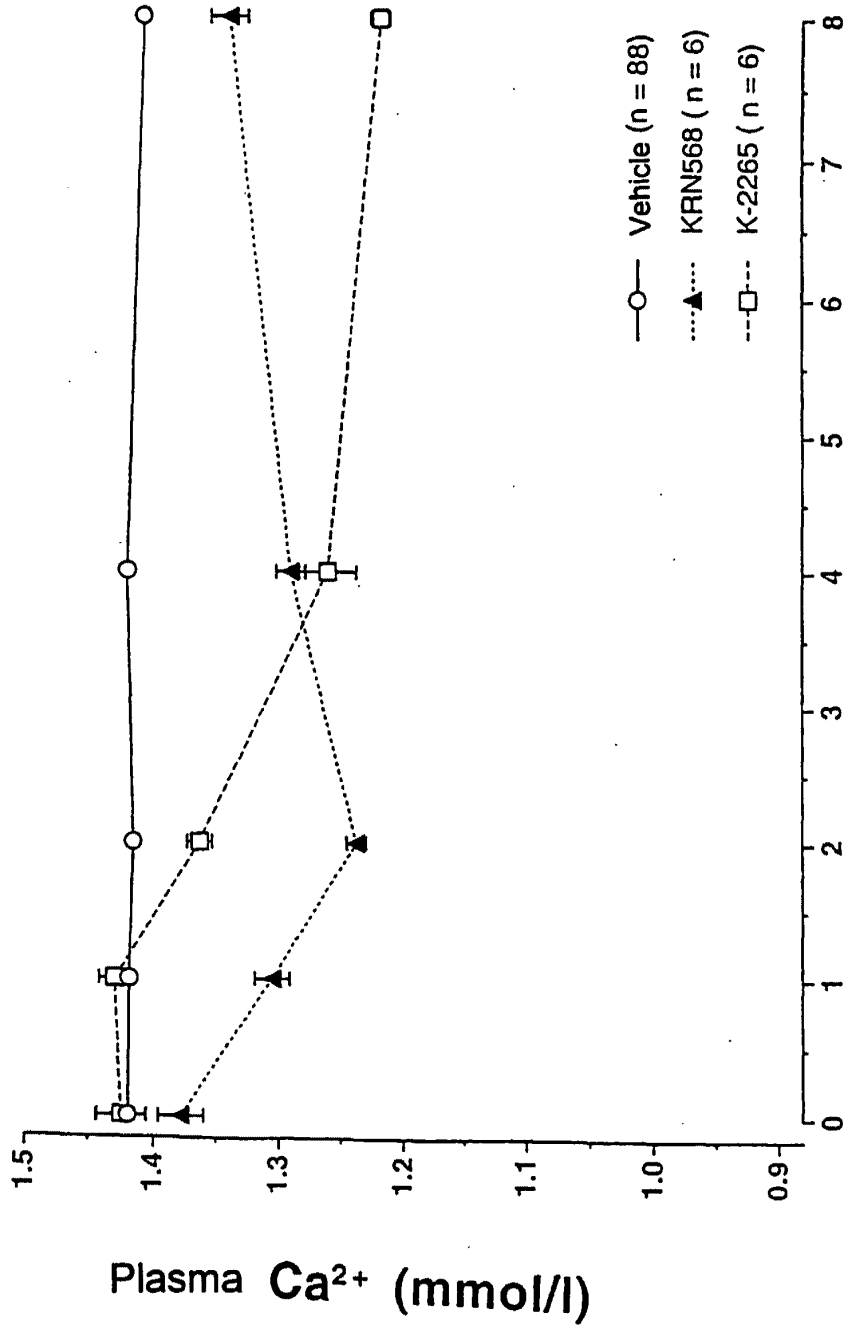

Vehicle (n = 88)
KRN568 (n = 6)
K-2265 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)

Fig. 61

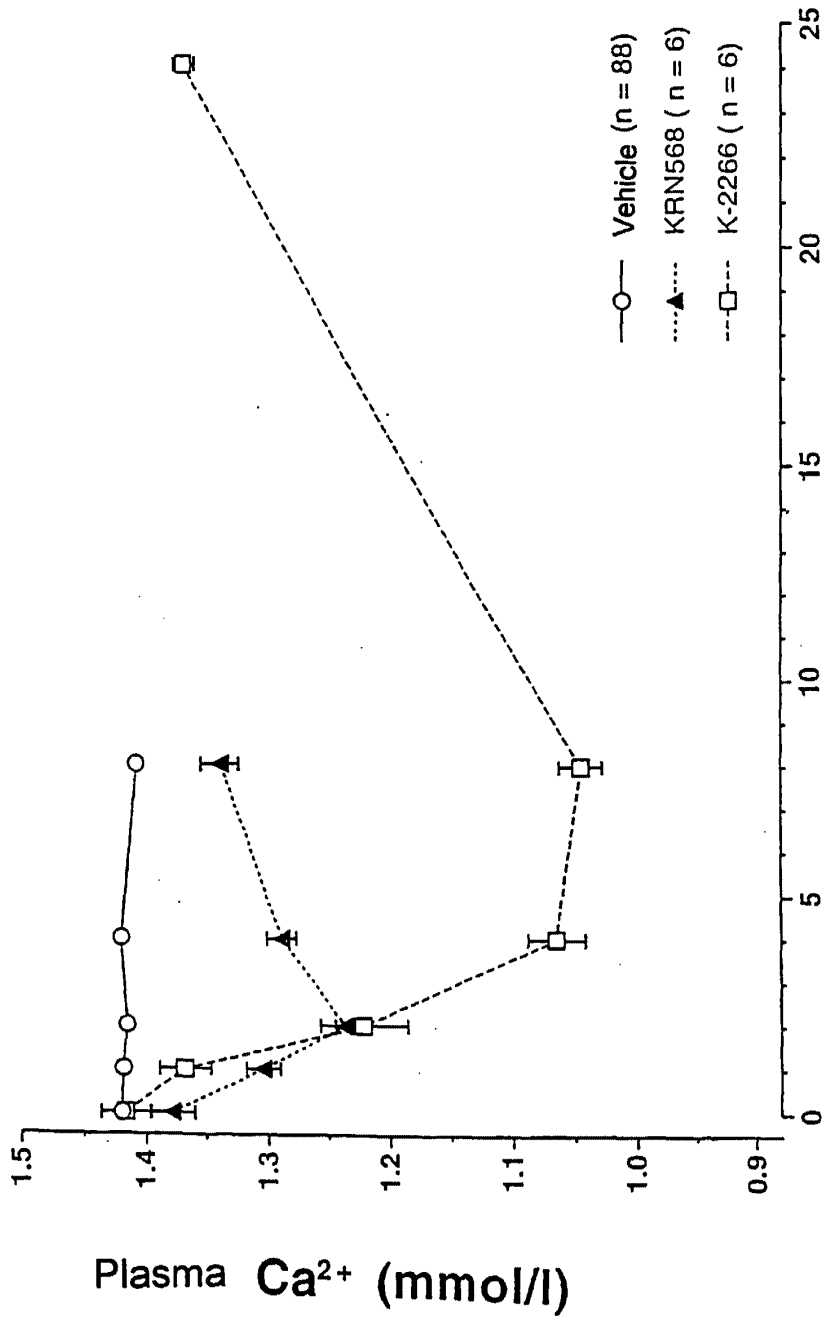

Vehicle (n = 88)
KRN568 (n = 6)
K-2266 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
Time (hr)

Fig. 62

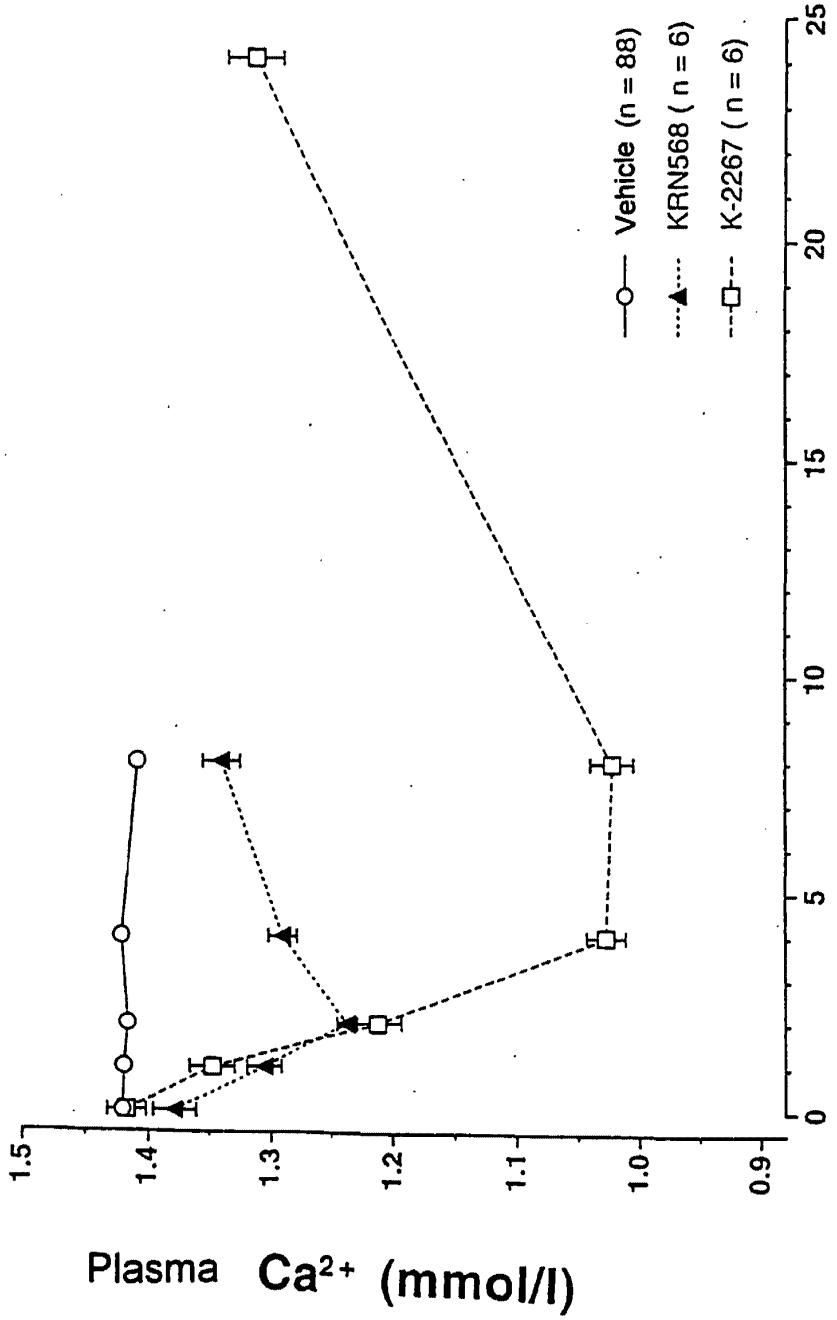

Vehicle (n = 88)
KRN568 (n = 6)
K-2267 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25

Fig. 63

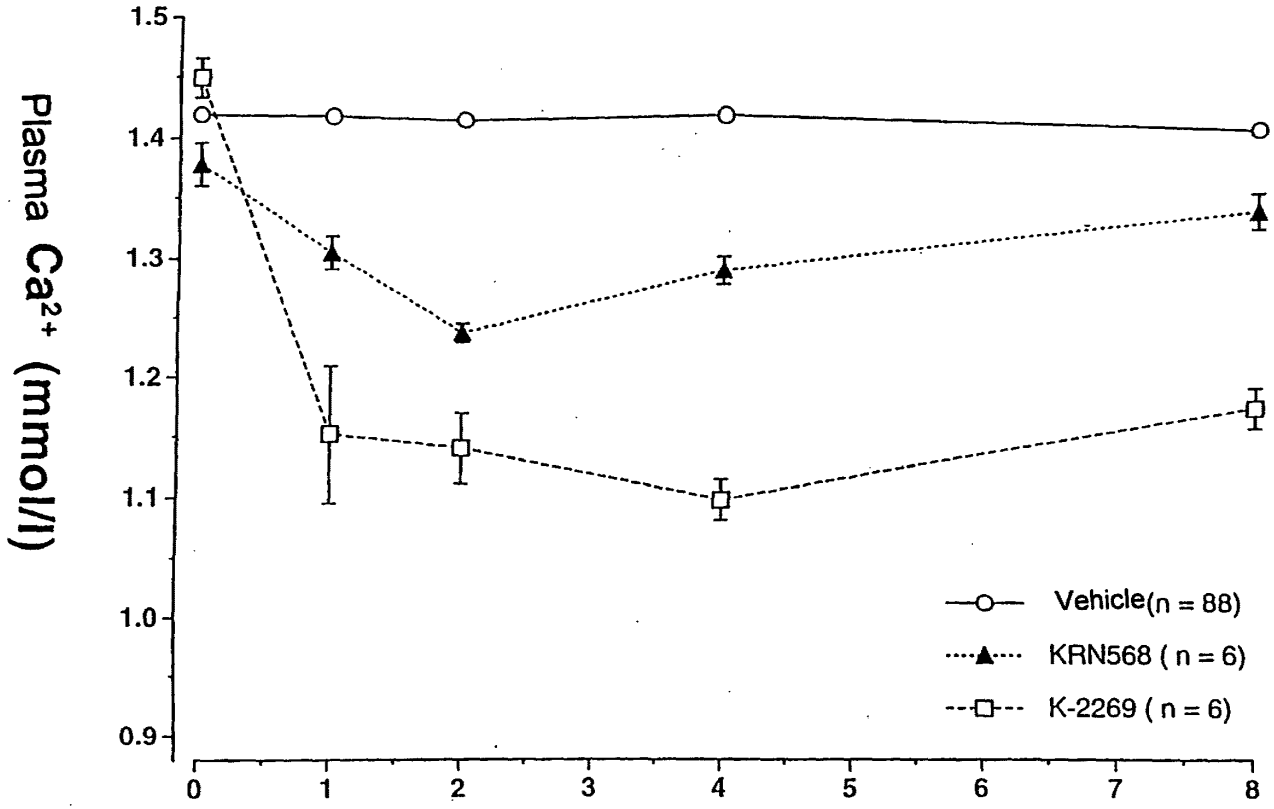

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle(n = 88)
KRN568 (n = 6)
K-2269 (n = 6)

Fig. 64

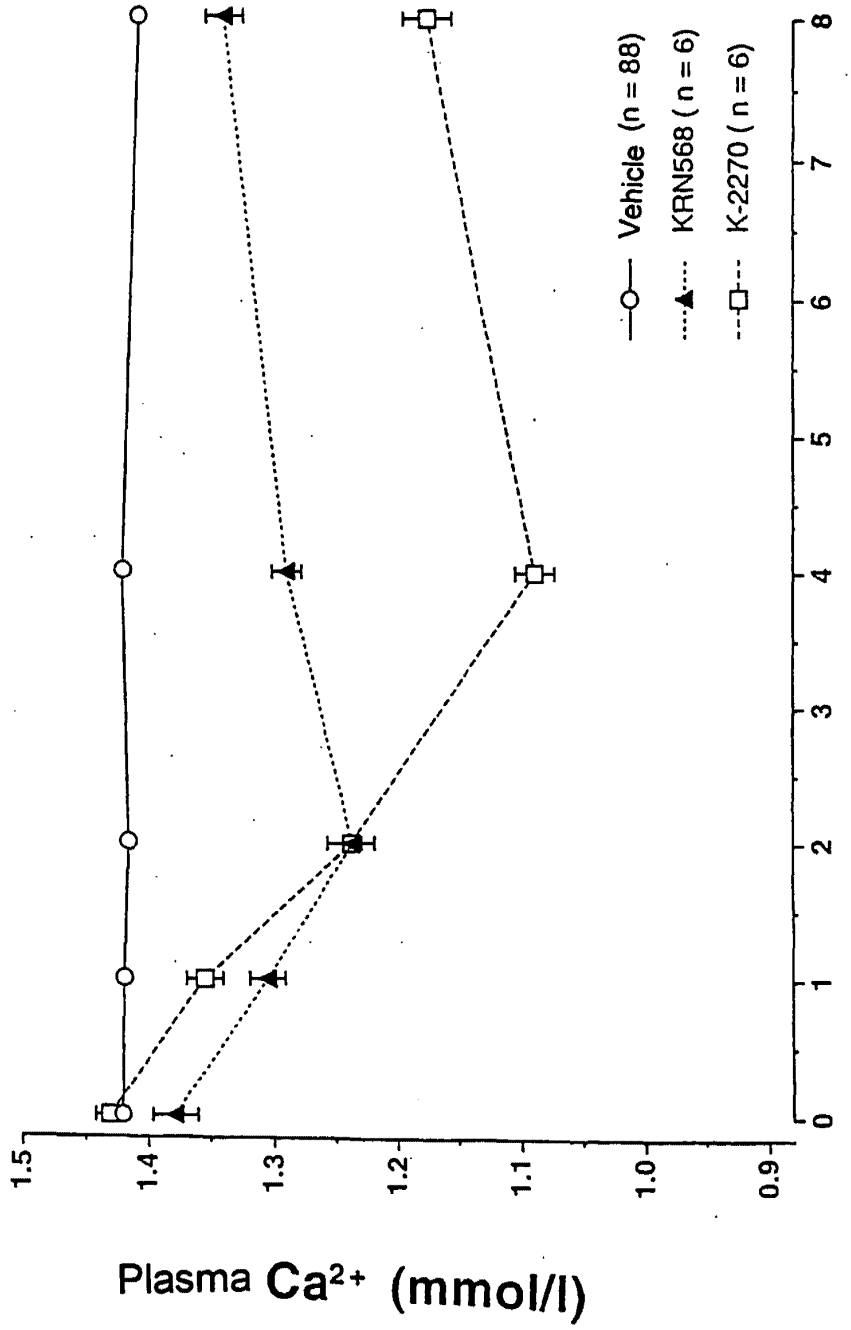

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2270 (n = 6)

Fig. 65

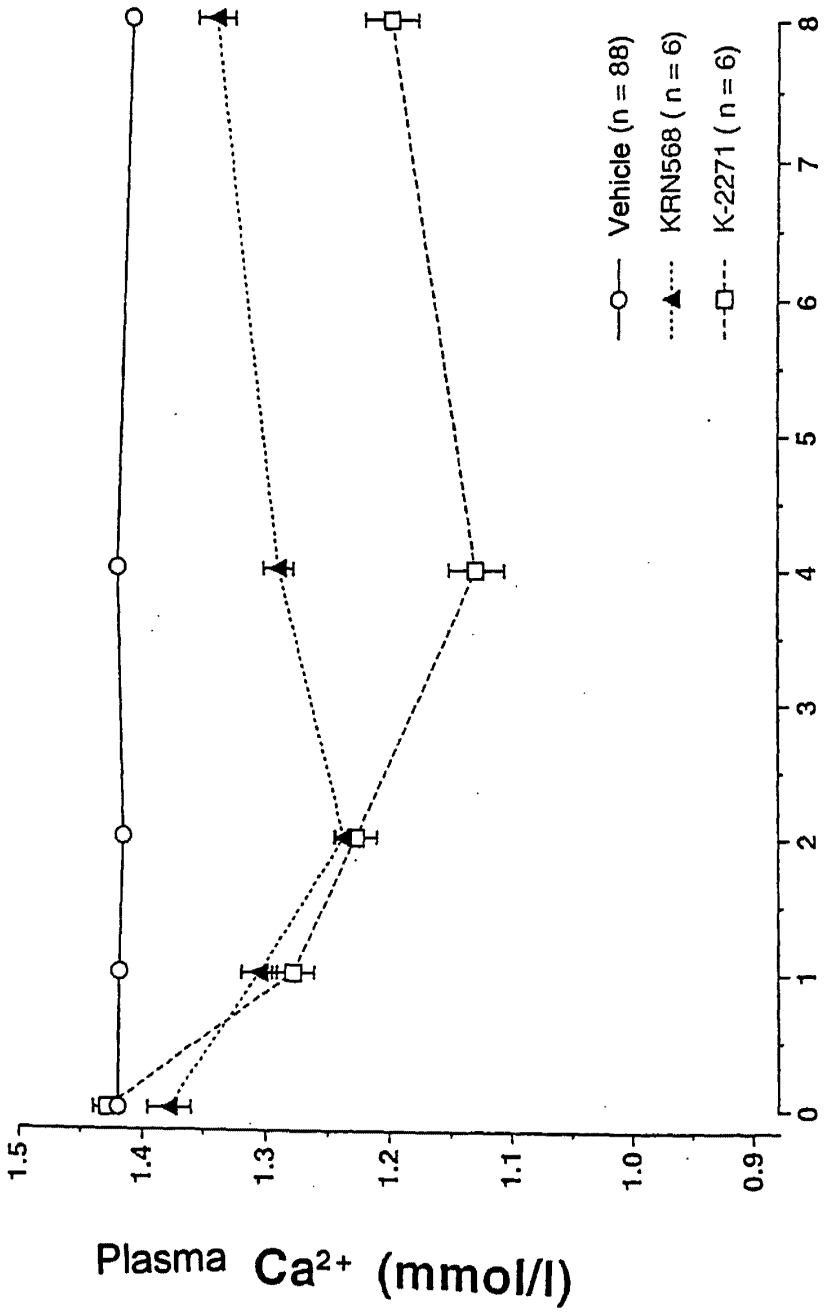

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2271 (n = 6)

Fig. 66

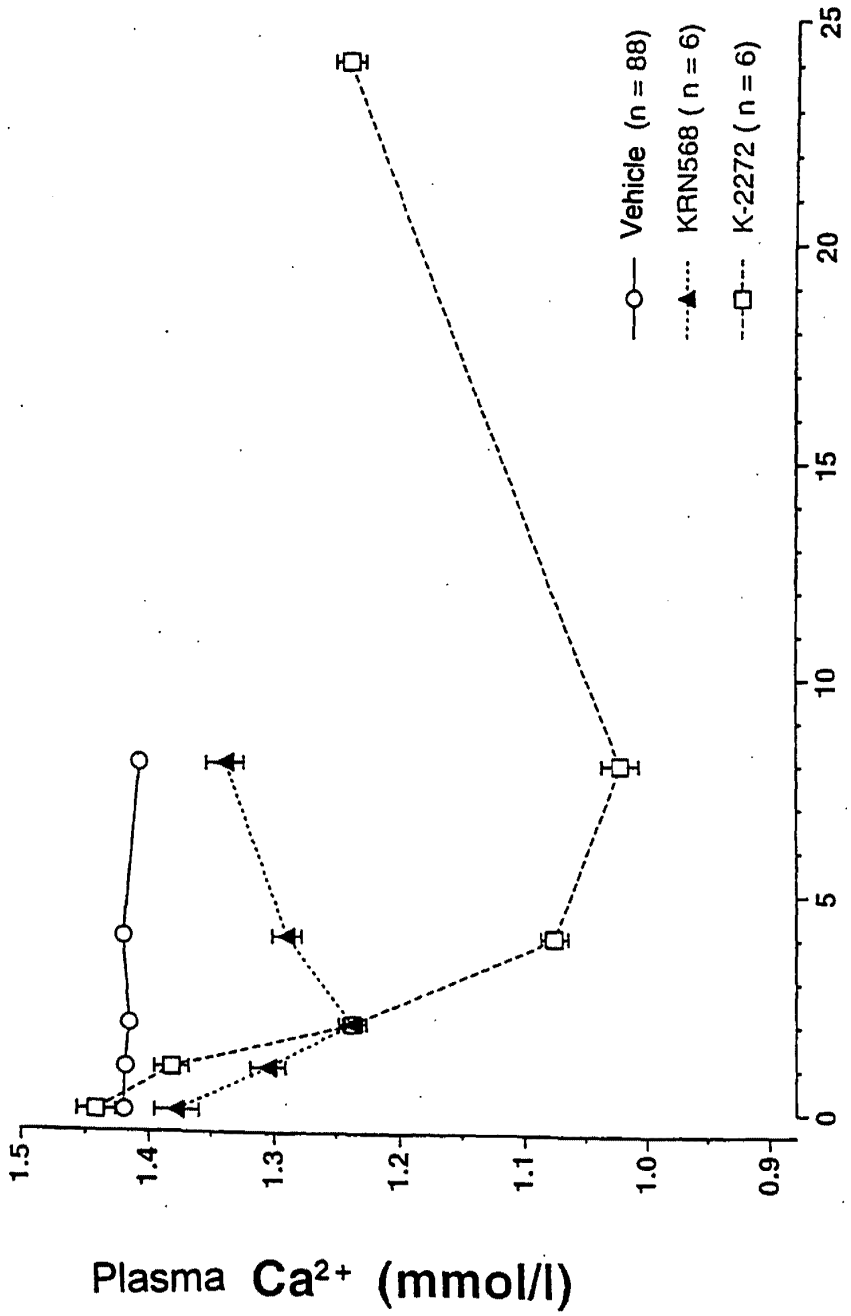

Vehicle (n = 88)
KRN568 (n = 6)
K-2272 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25

Fig. 67

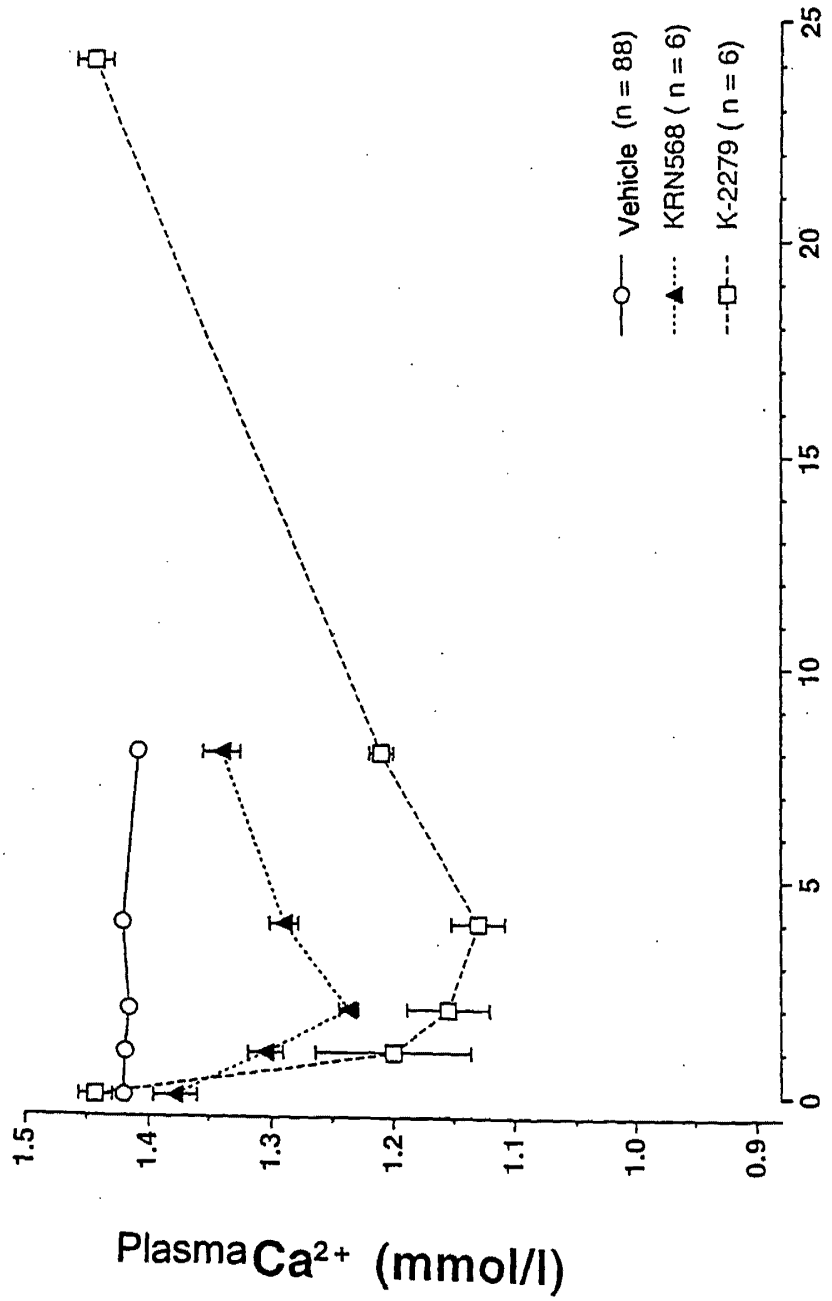

Vehicle (n = 88)
KRN568 (n = 6)
K-2279 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25

Fig. 68

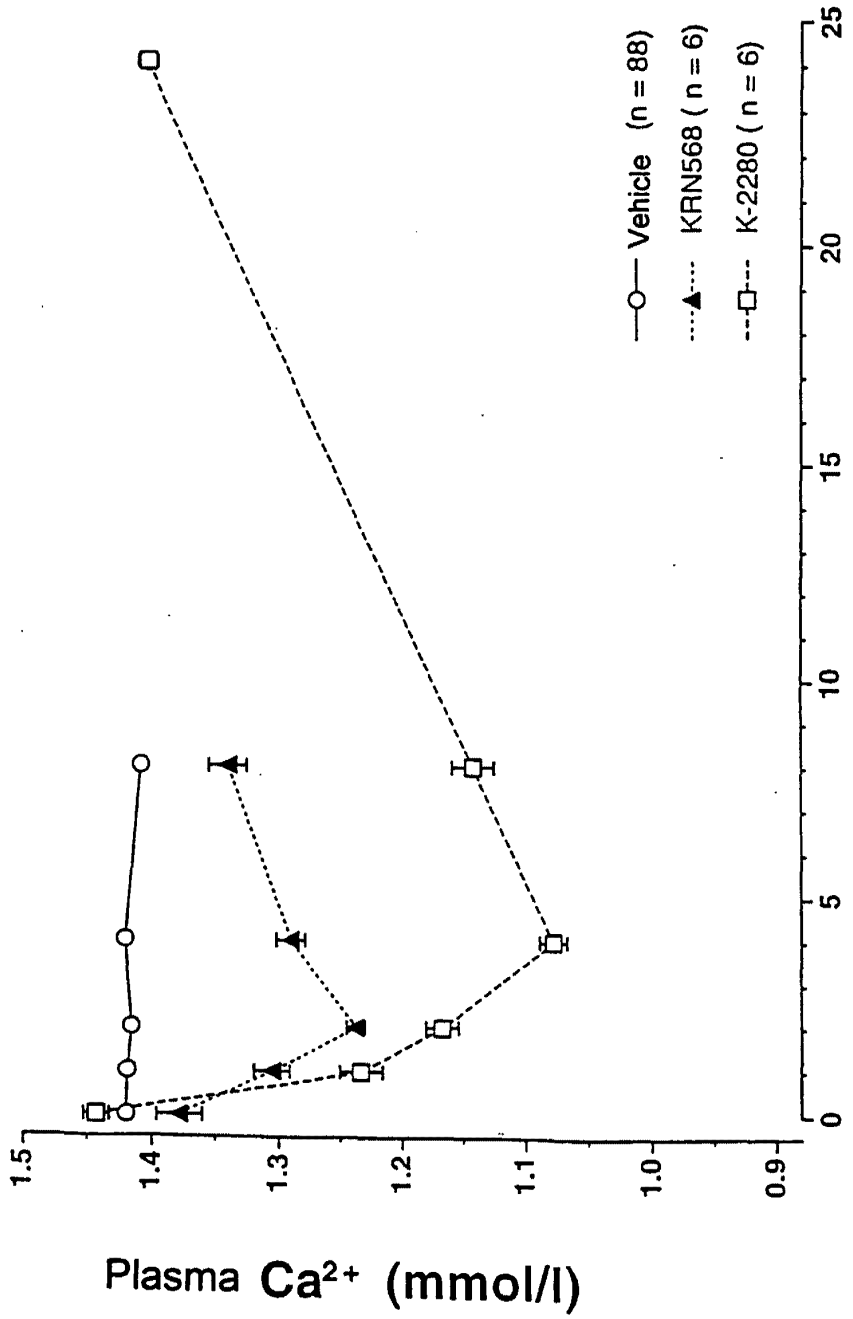

Vehicle (n = 88)
KRN568 (n = 6)
K-2280 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25

Fig. 69

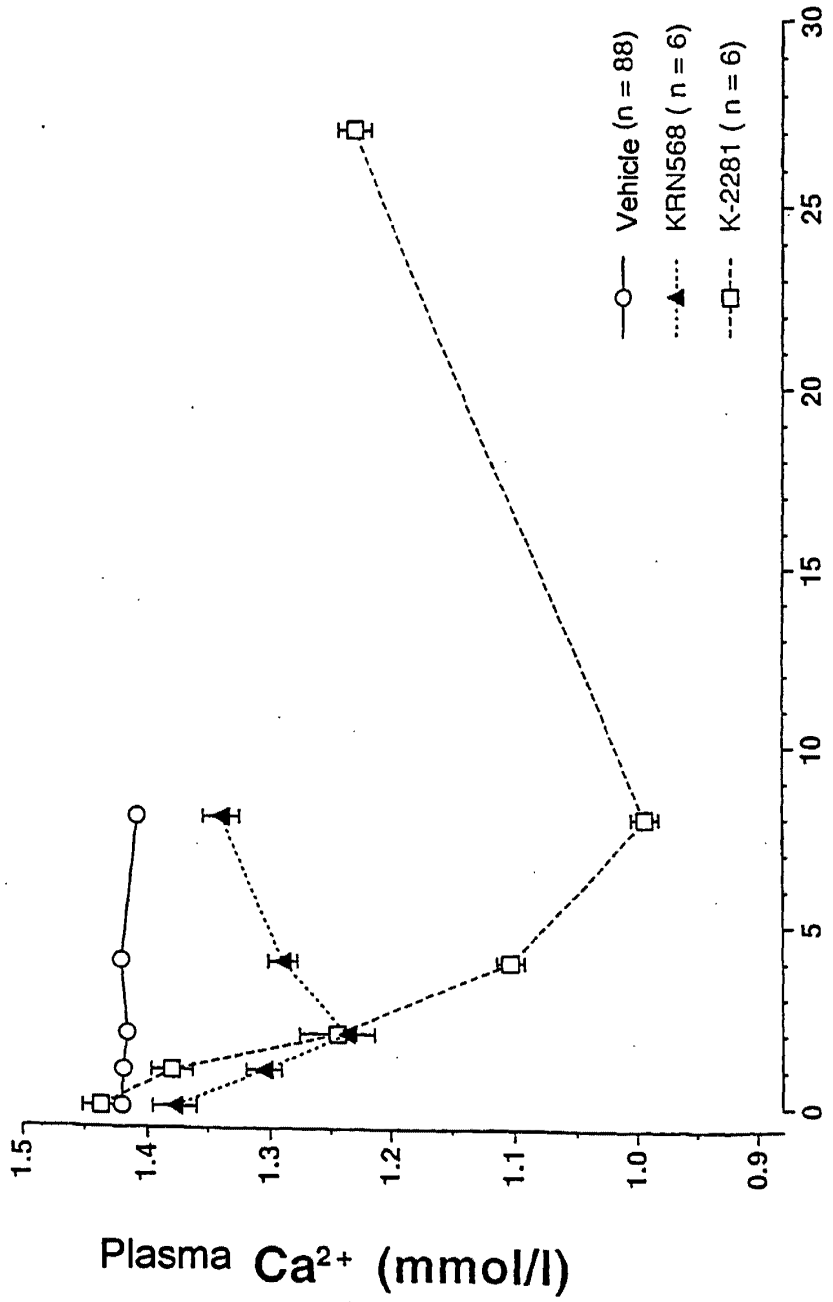

Vehicle (n = 88)
KRN568 (n = 6)
K-2281 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30
Time (hr)

Fig. 70

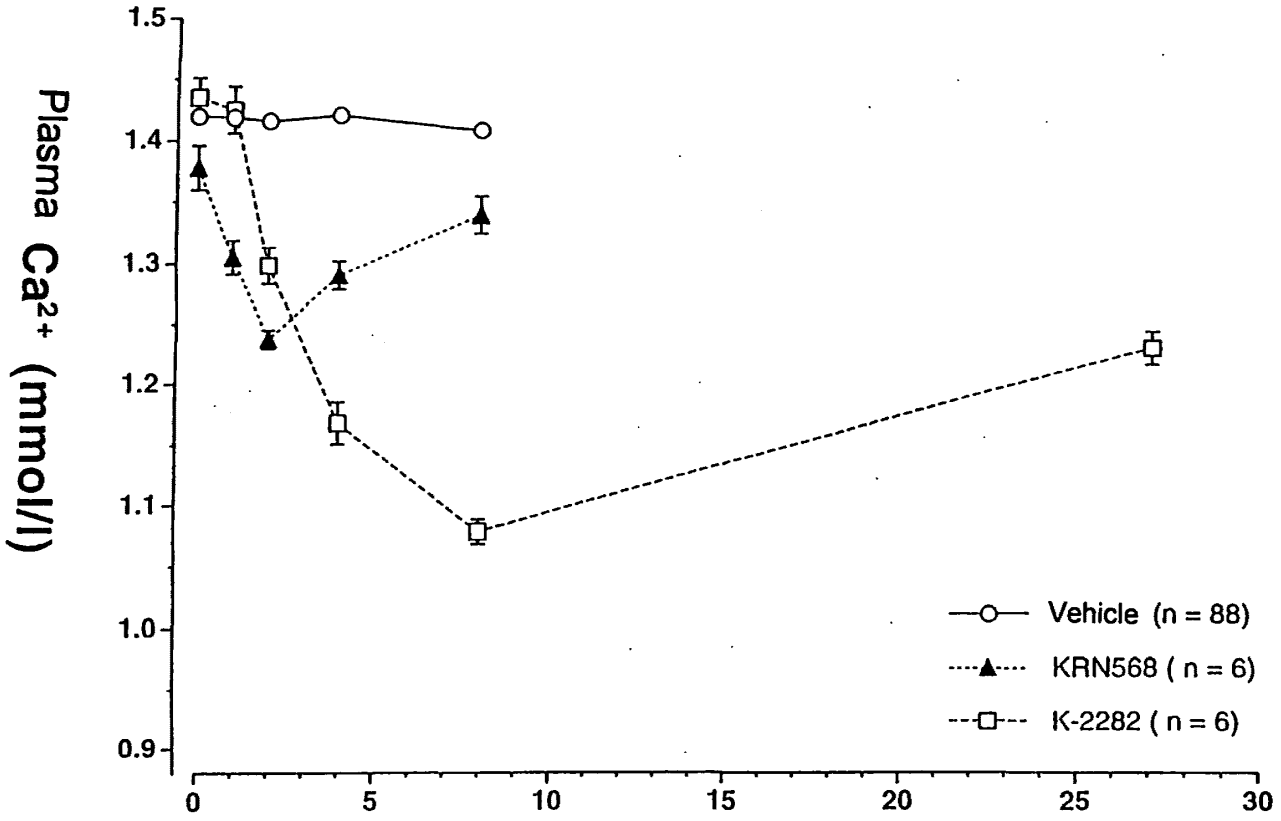

Plasma Ca^{2+} (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2282 (n = 6)

Fig. 71

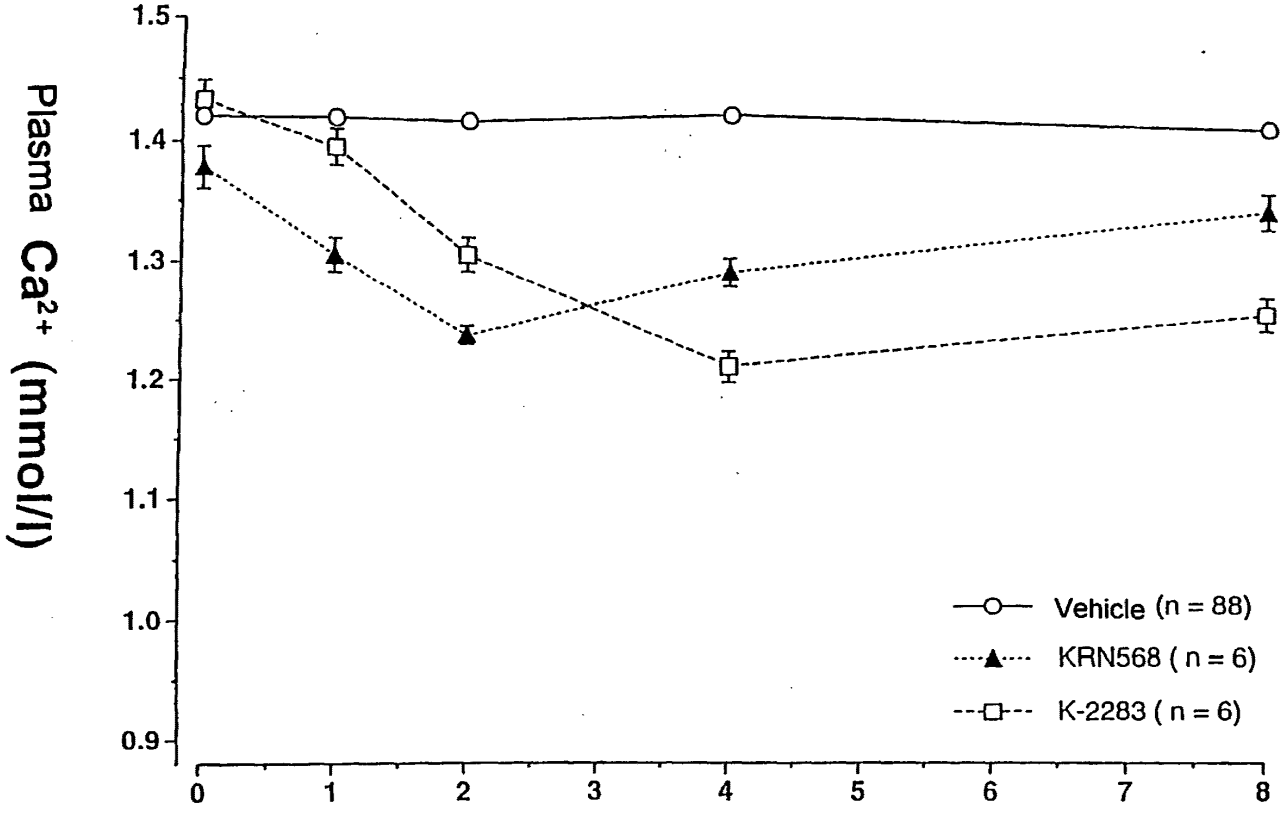

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2283 (n = 6)

Fig. 72

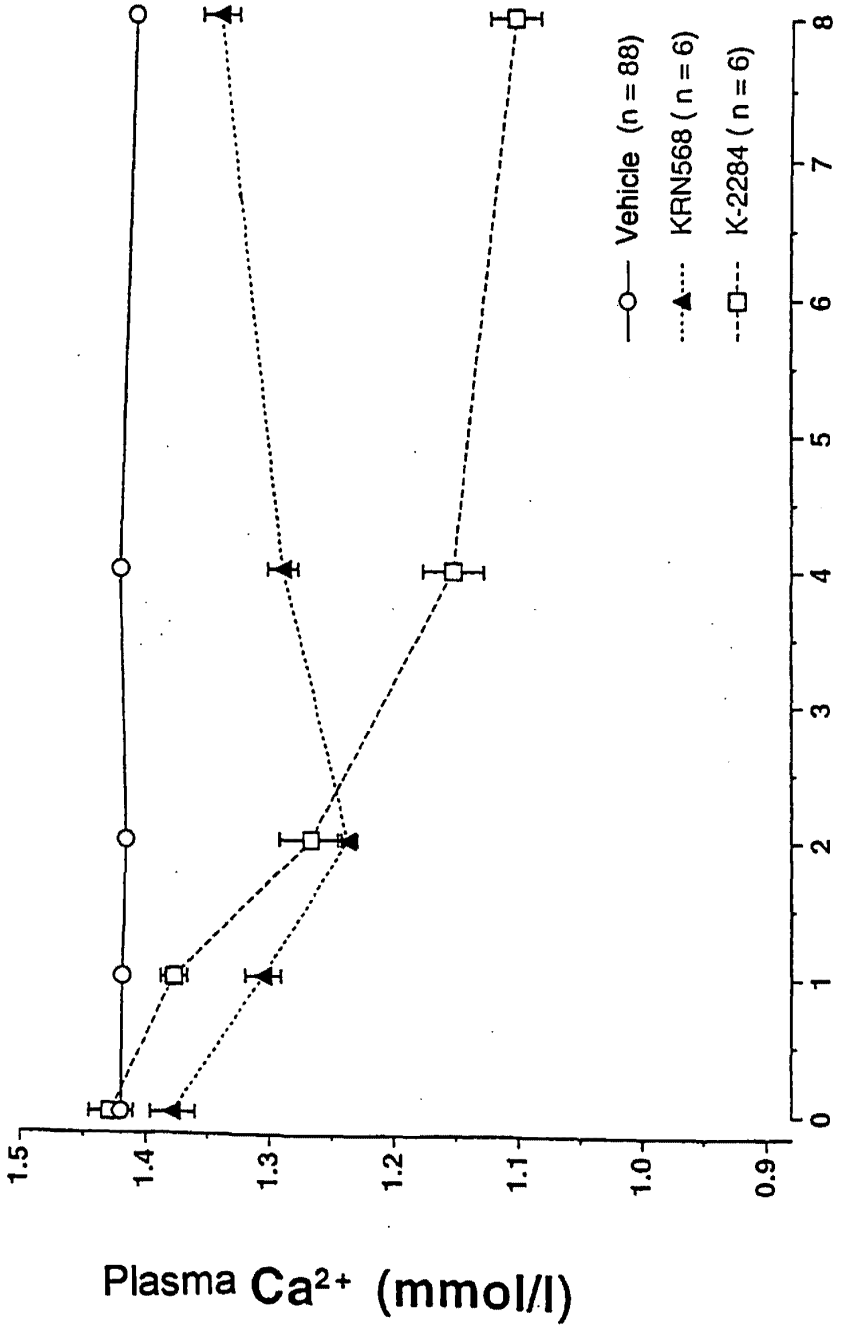

Vehicle (n = 88)
KRN568 (n = 6)
K-2284 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)

Fig. 73

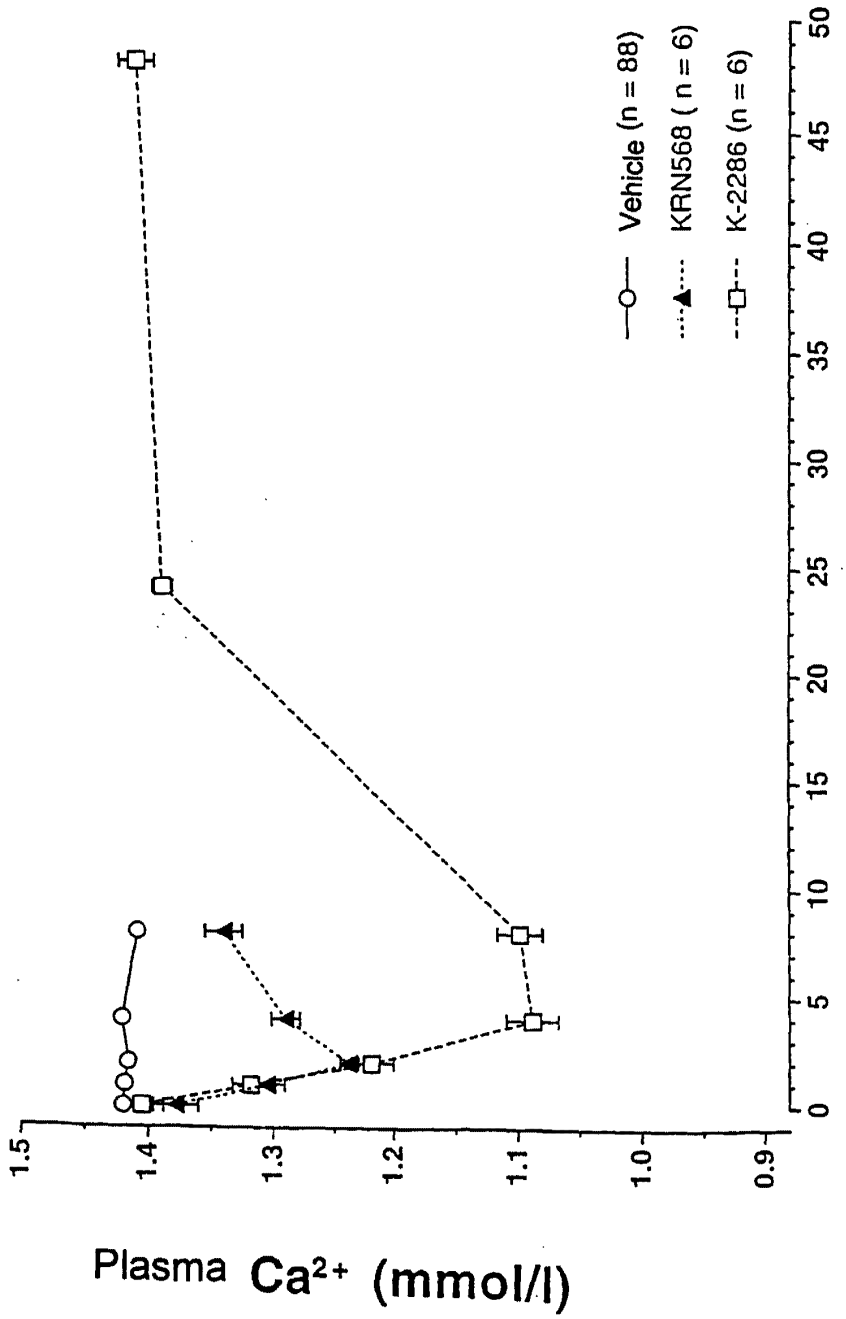

Vehicle (n = 88)
KRN568 (n = 6)
K-2286 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30
35
40
45
50

Fig. 74

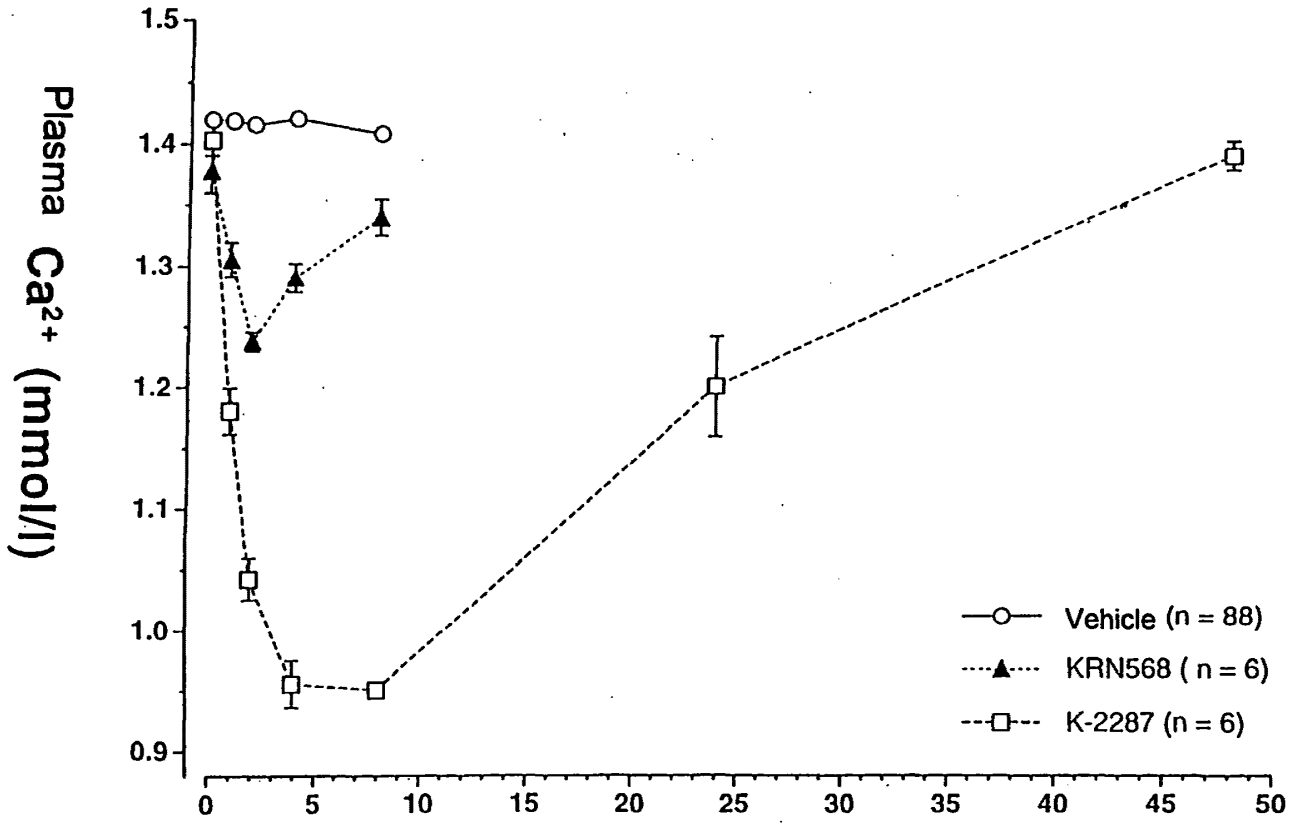

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30
35
40
45
50
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2287 (n = 6)

Fig. 75

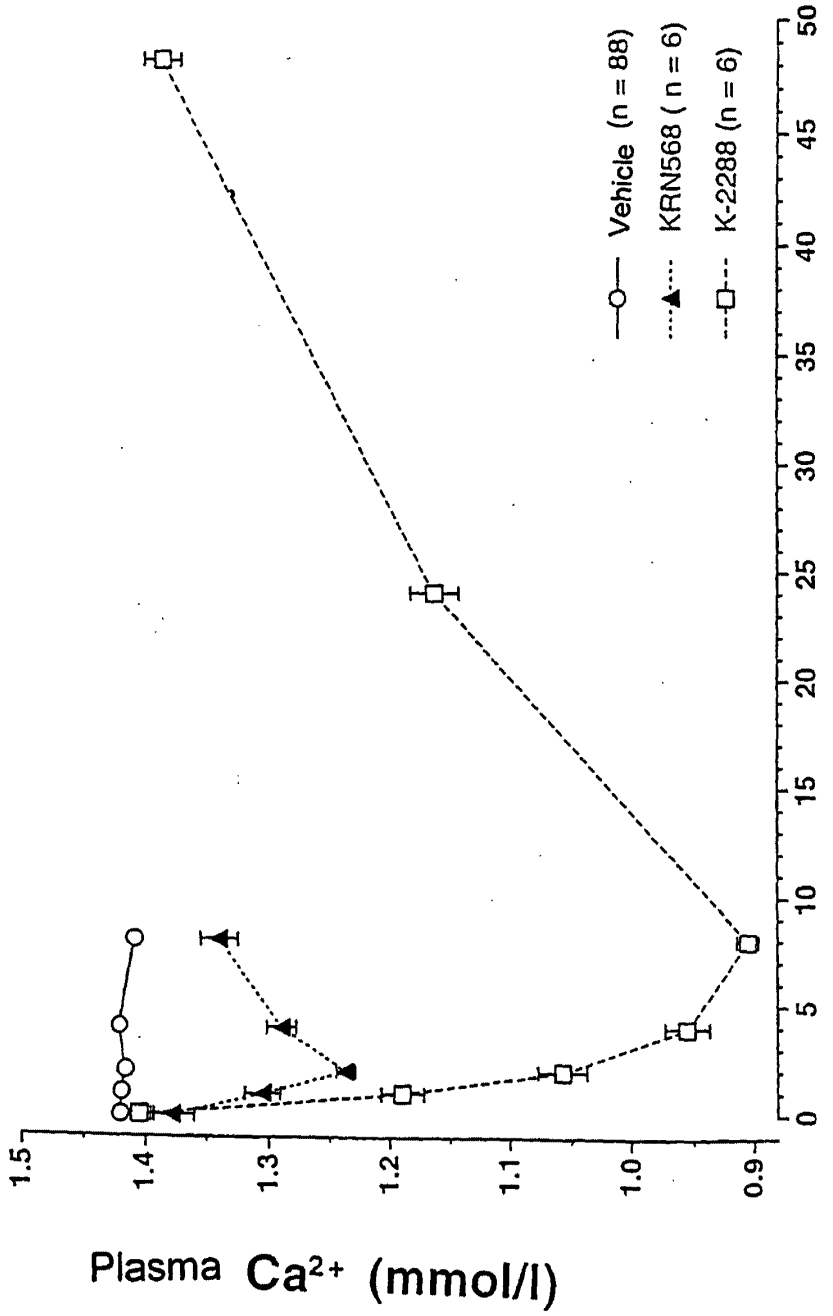

Vehicle (n = 88)
KRN568 (n = 6)
K-2288 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30
35
40
45
50
Time (hr)

Fig. 76

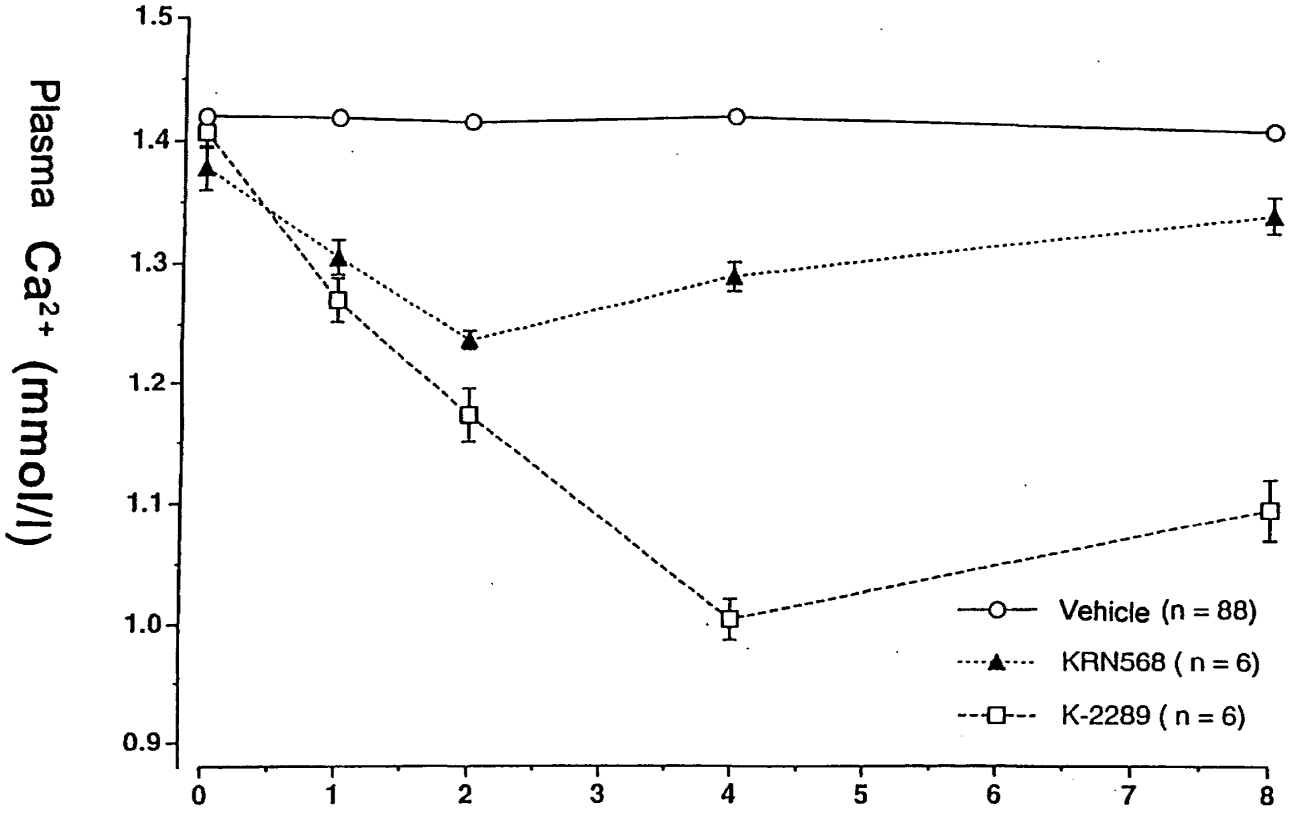

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2289 (n = 6)

Fig. 77

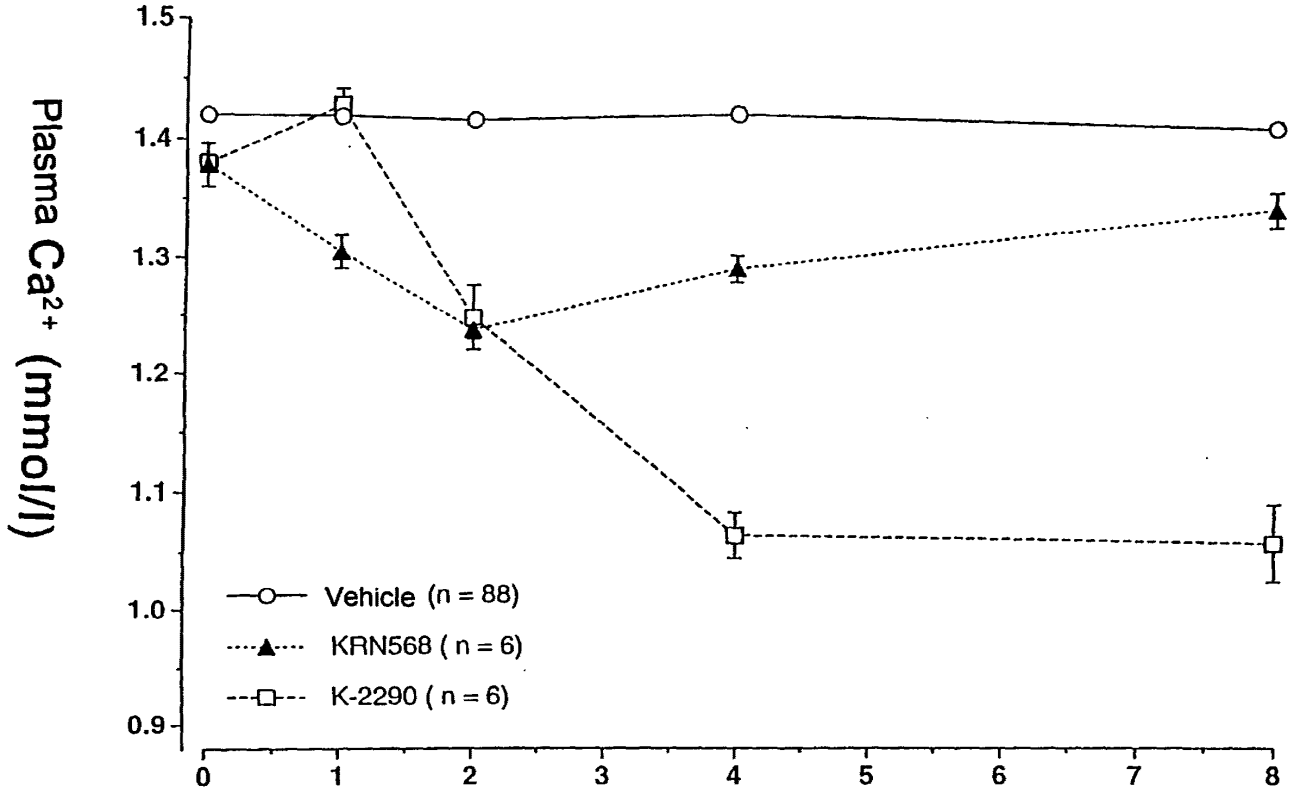

Plasma Ca^{2+} (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Vehicle (n = 88)
KRN568 (n = 6)
K-2290 (n = 6)
Time (hr)

Fig. 78

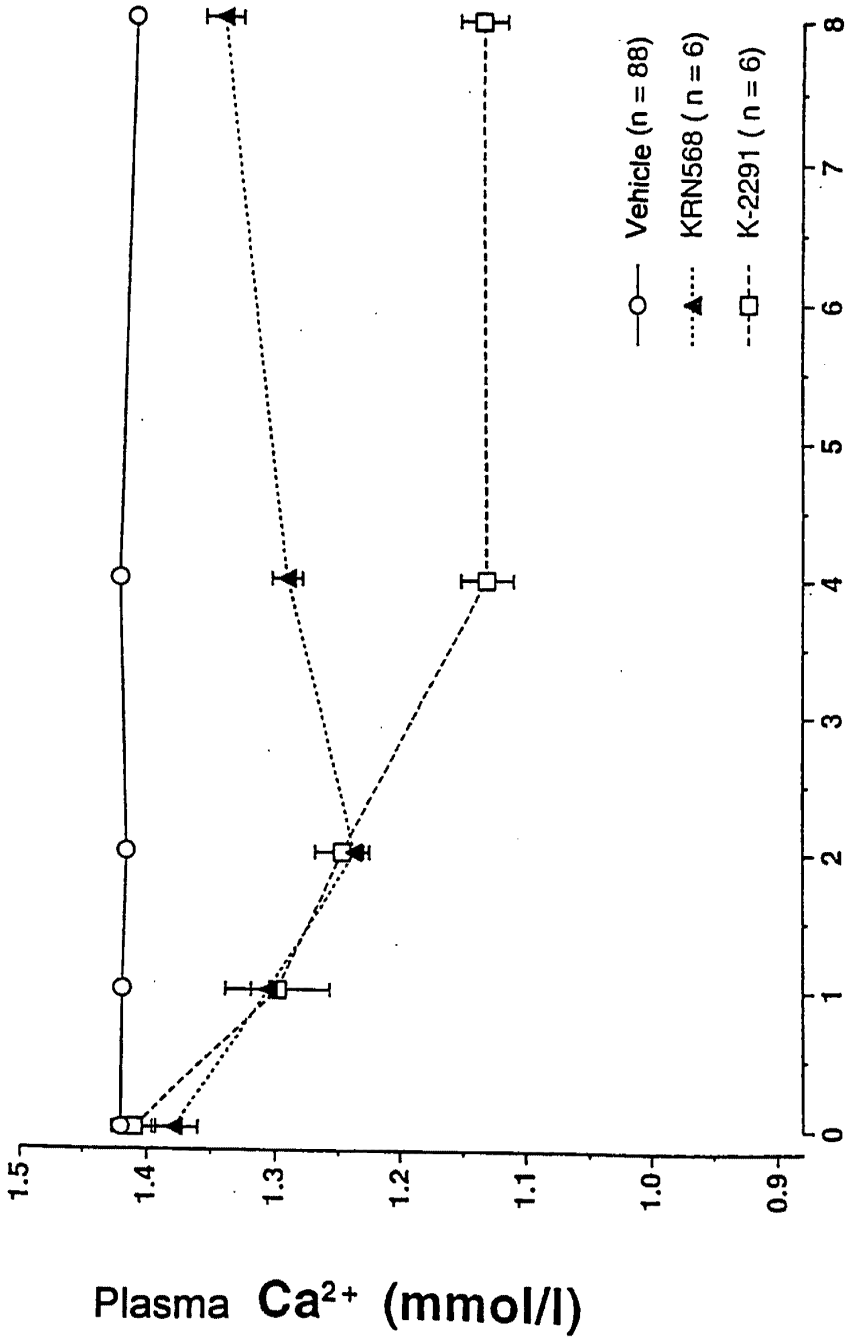

Vehicle (n = 88)
KRN568 (n = 6)
K-2291 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8

Fig. 79

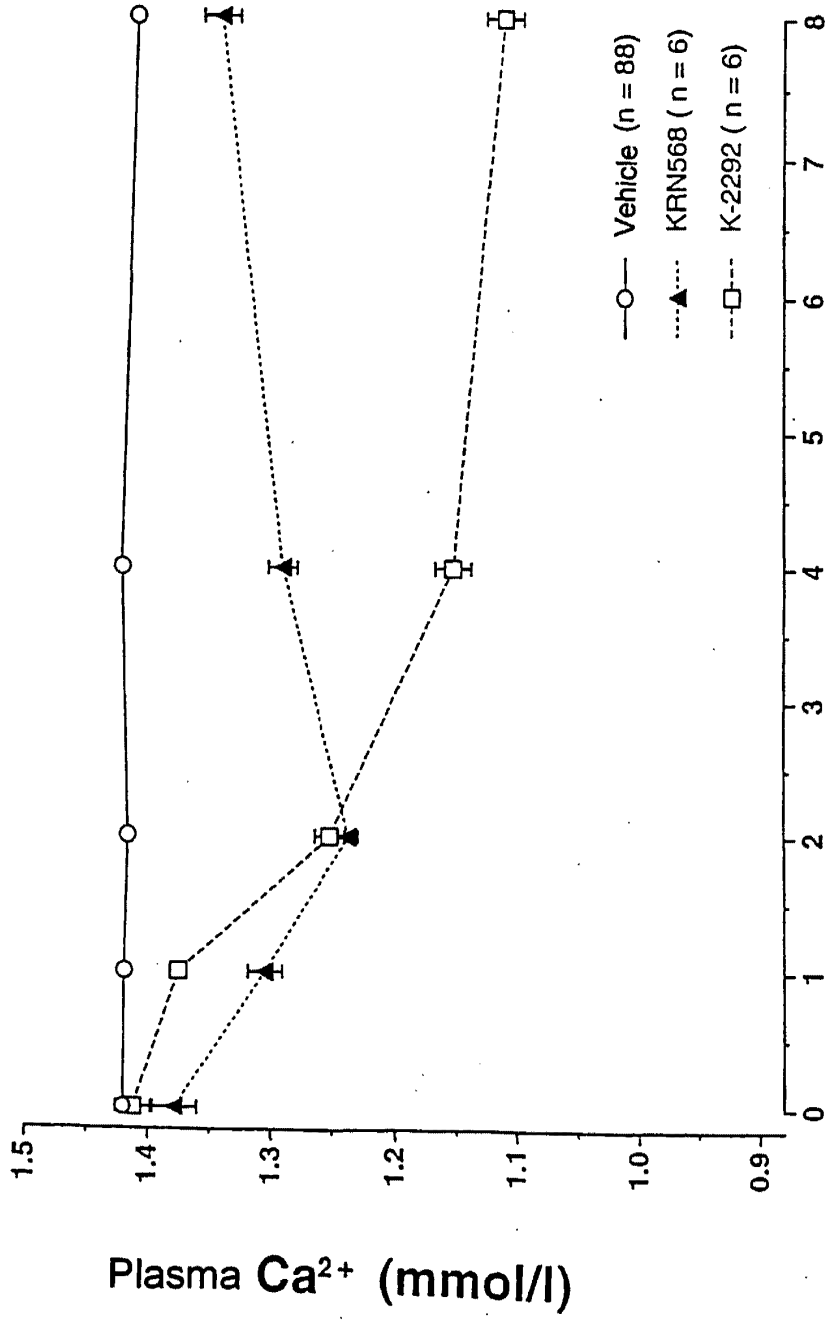

Plasma Ca^{2+} (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2292 (n = 6)

Fig. 80

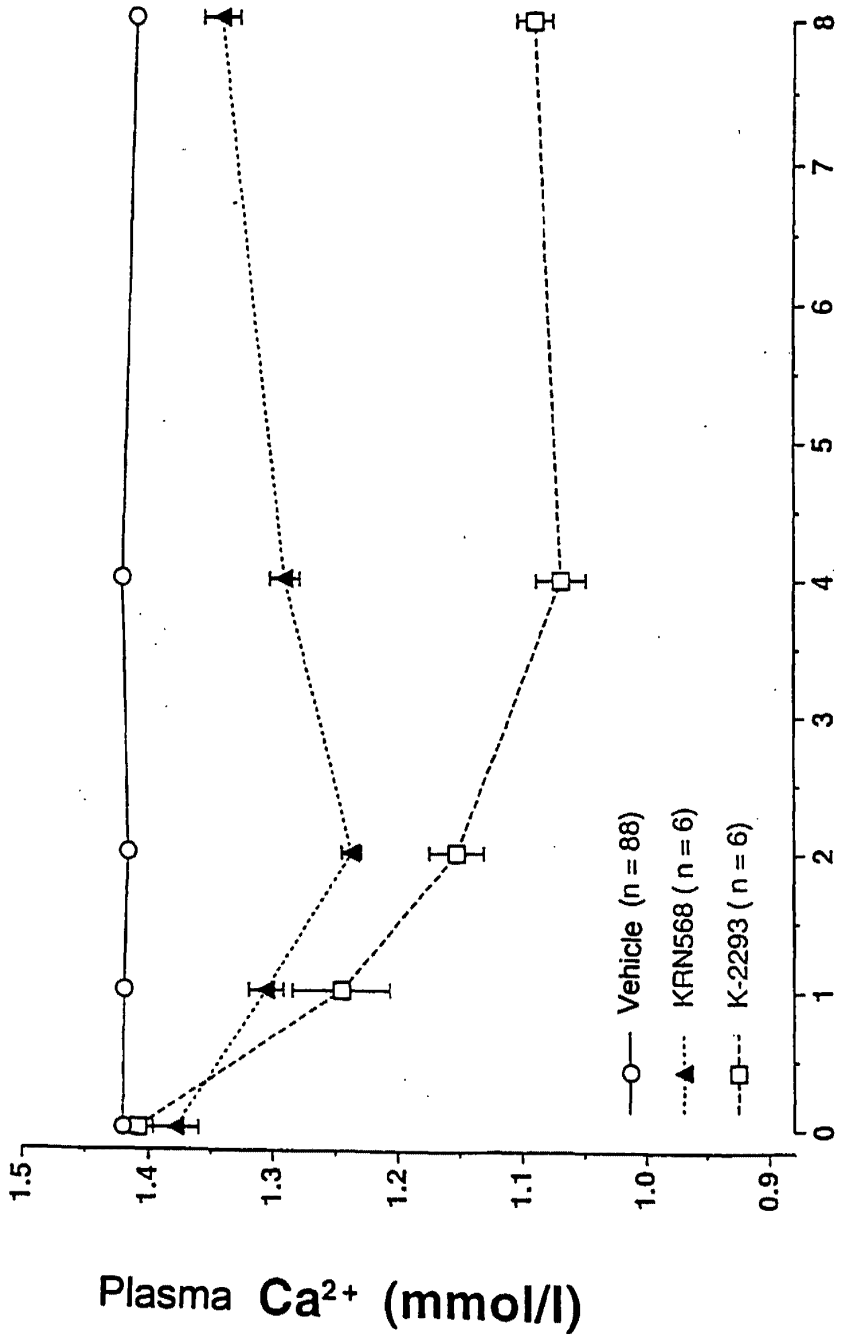

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2293 (n = 6)

Fig. 81

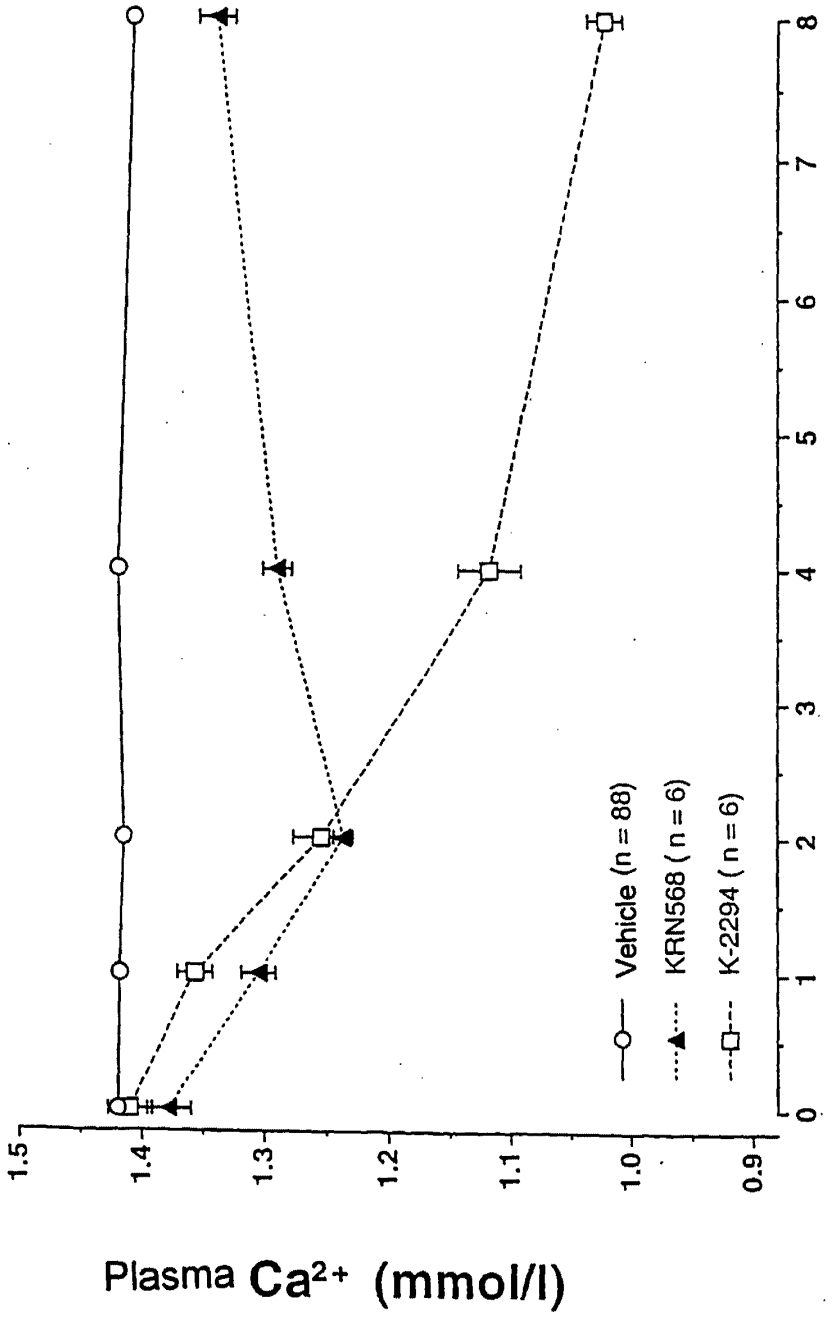

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2294 (n = 6)

Fig. 82

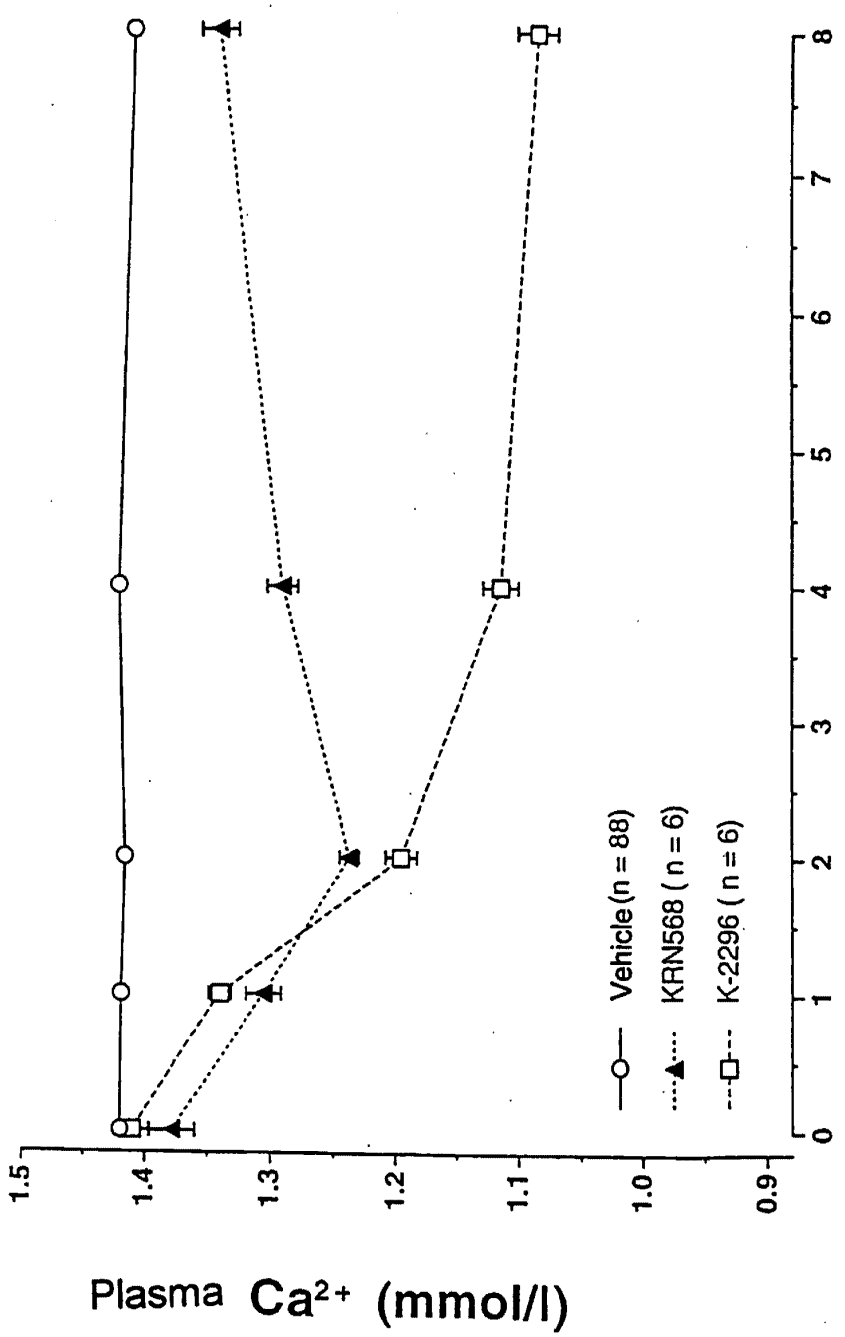

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2296 (n = 6)

Fig. 83

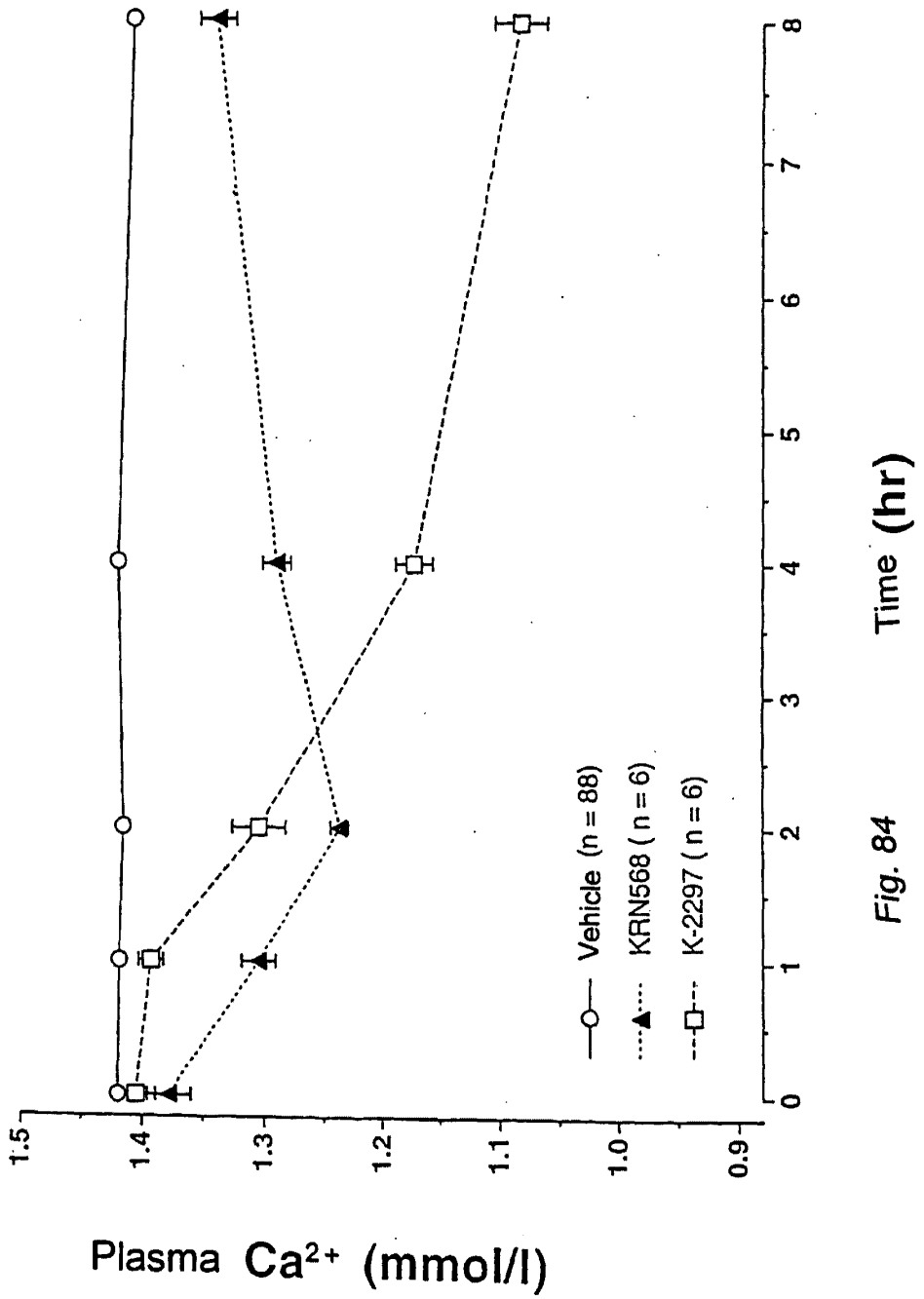

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2297 (n = 6)

Fig. 84

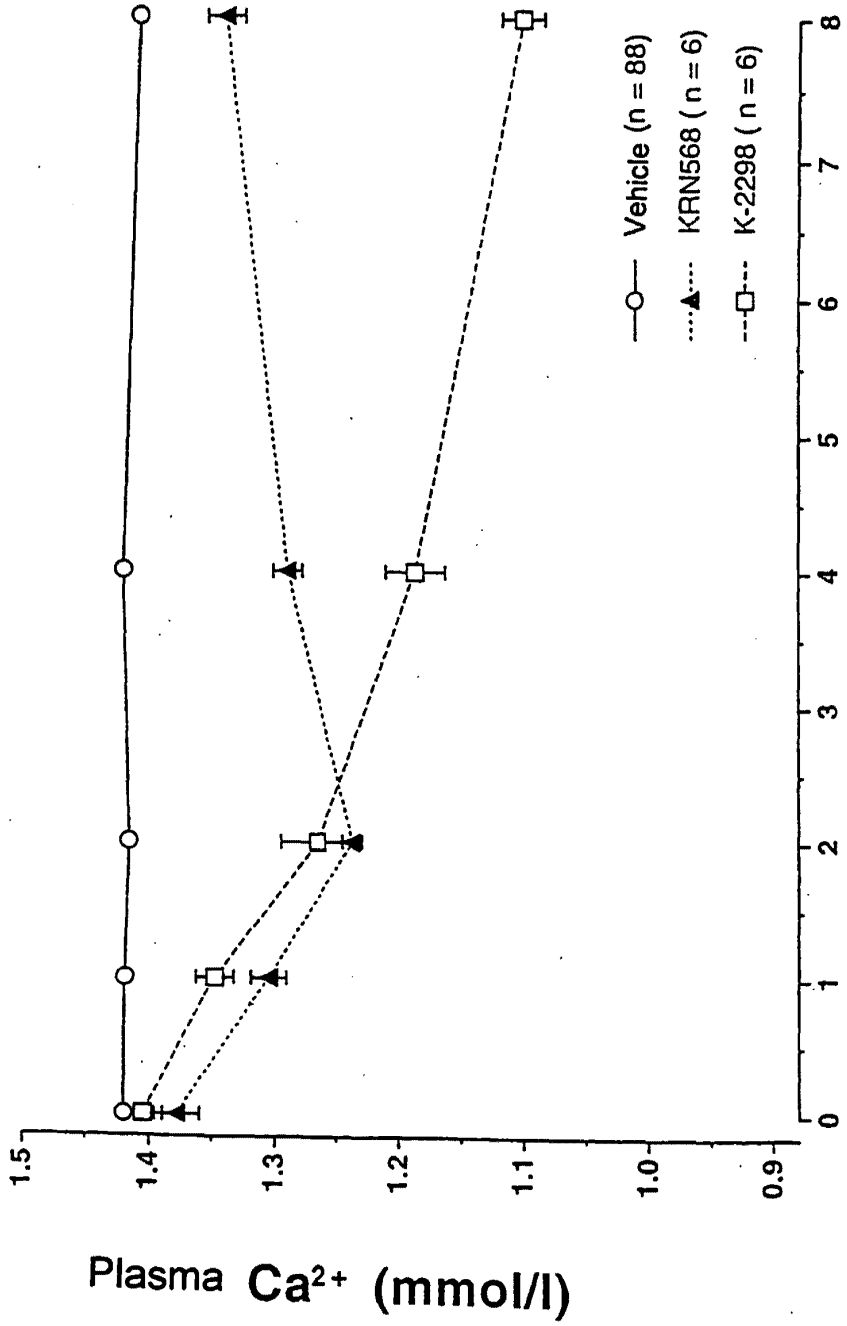

Vehicle (n = 88)
KRN568 (n = 6)
K-2298 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)

Fig. 85

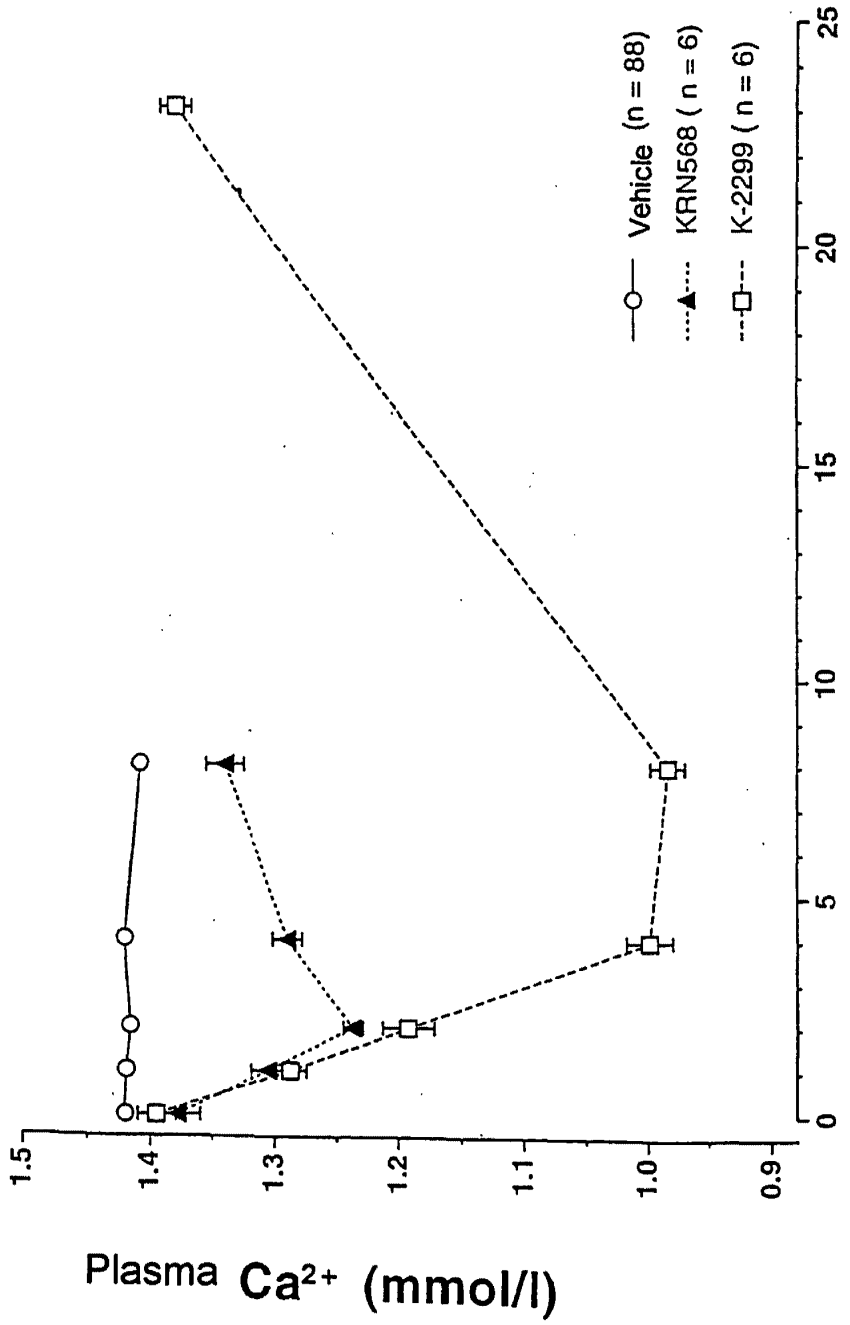

Vehicle (n = 88)
KRN568 (n = 6)
K-2299 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25

Fig. 86

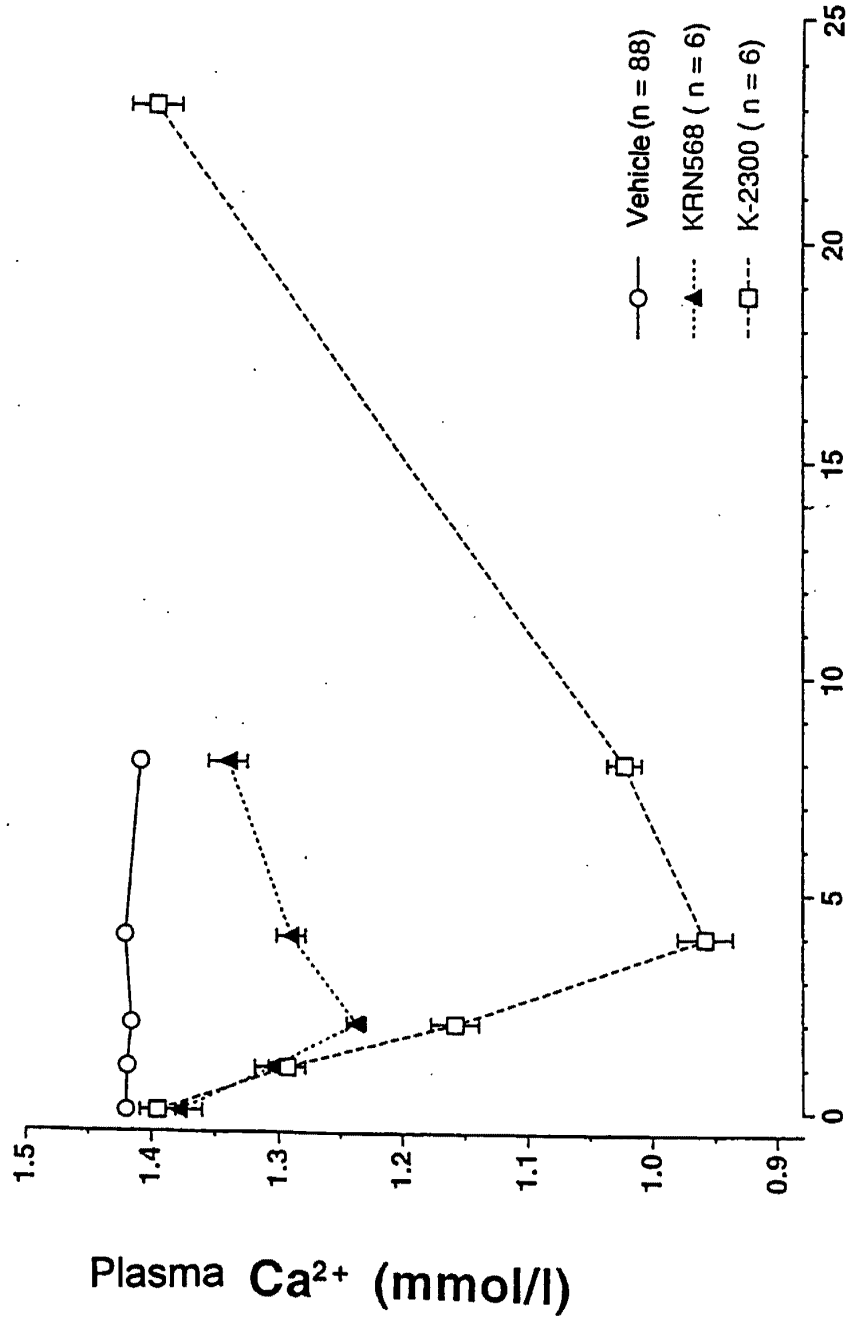

Vehicle (n = 88)
KRN568 (n = 6)
K-2300 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
Time (hr)

Fig. 87

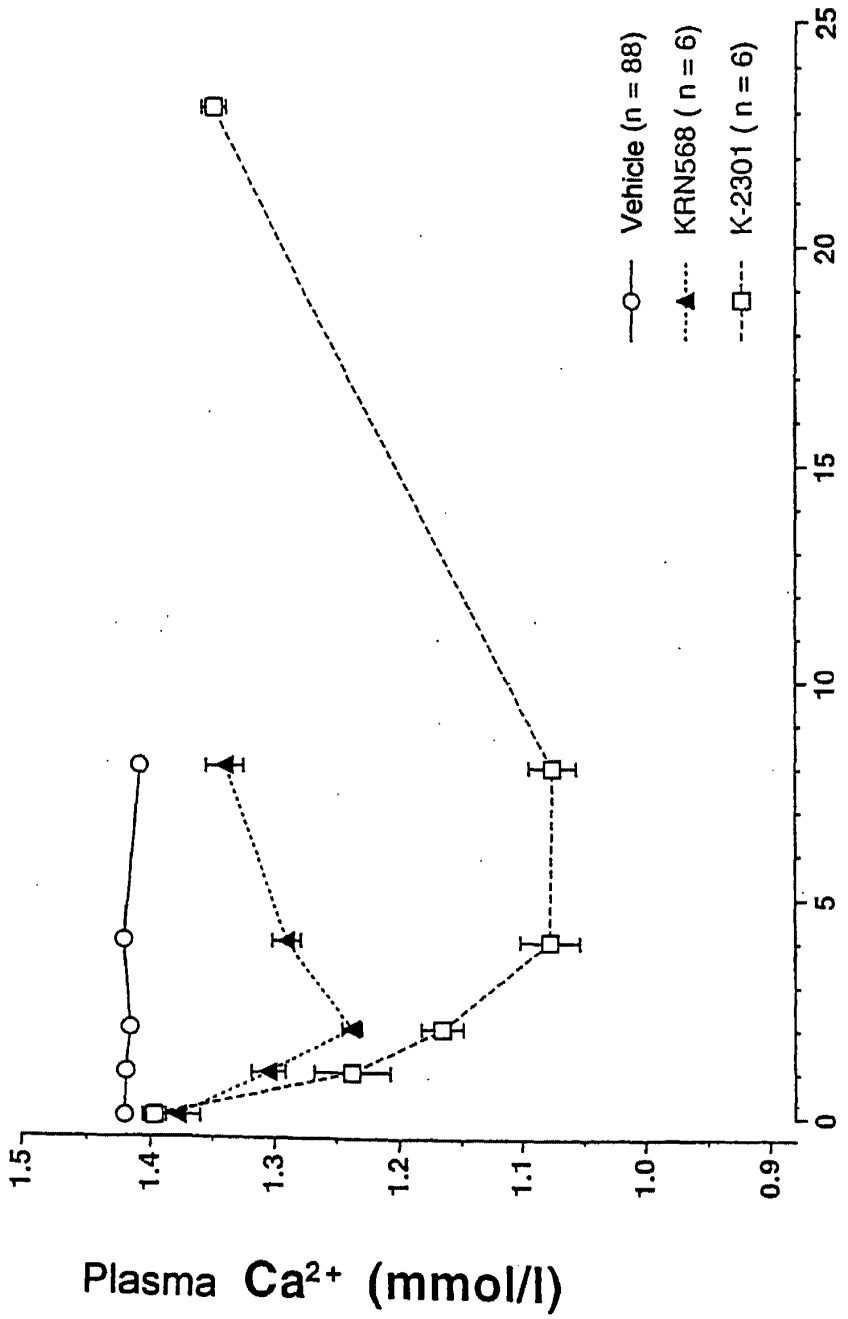

Vehicle (n = 88)
KRN568 (n = 6)
K-2301 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
Time (hr)

Fig. 88

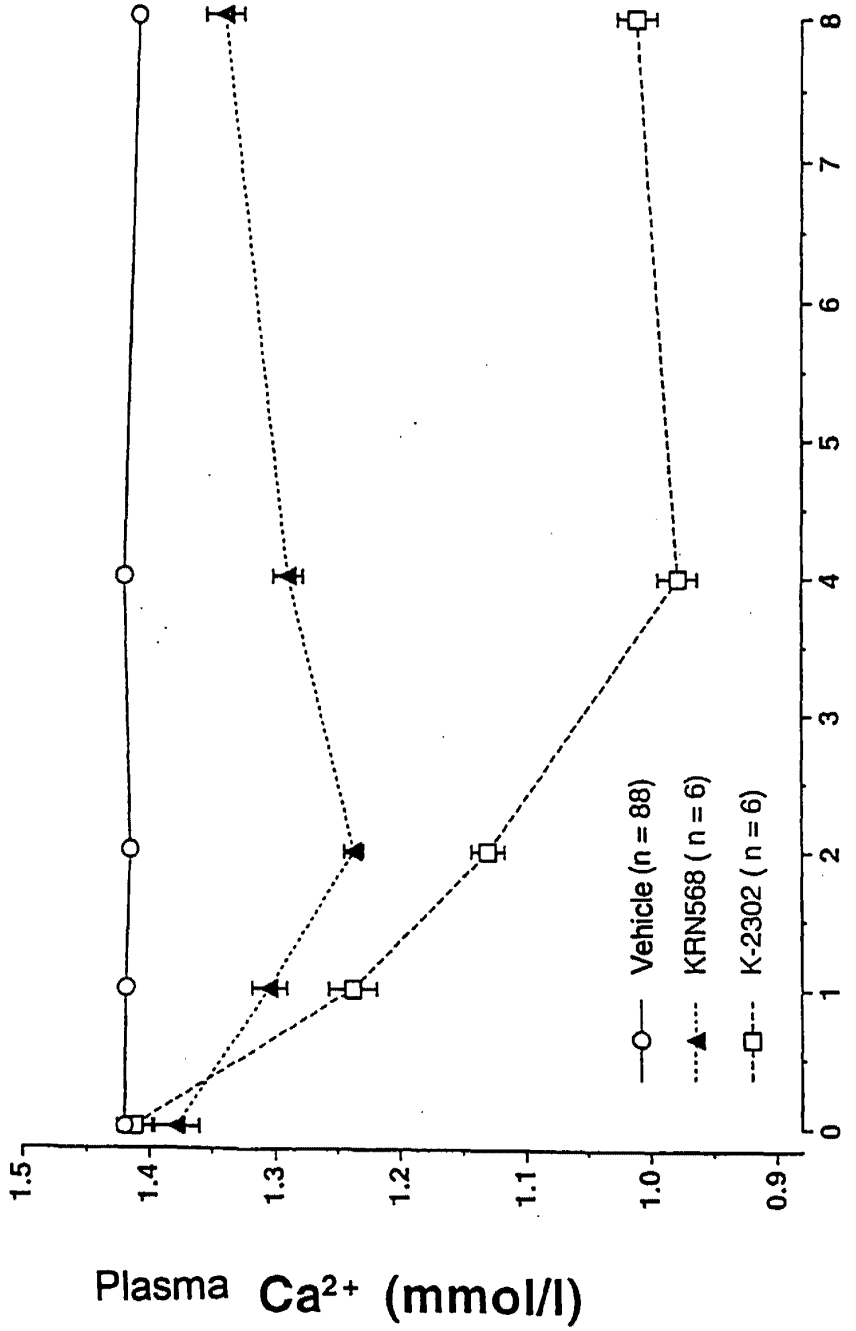

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2302 (n = 6)

Fig. 89

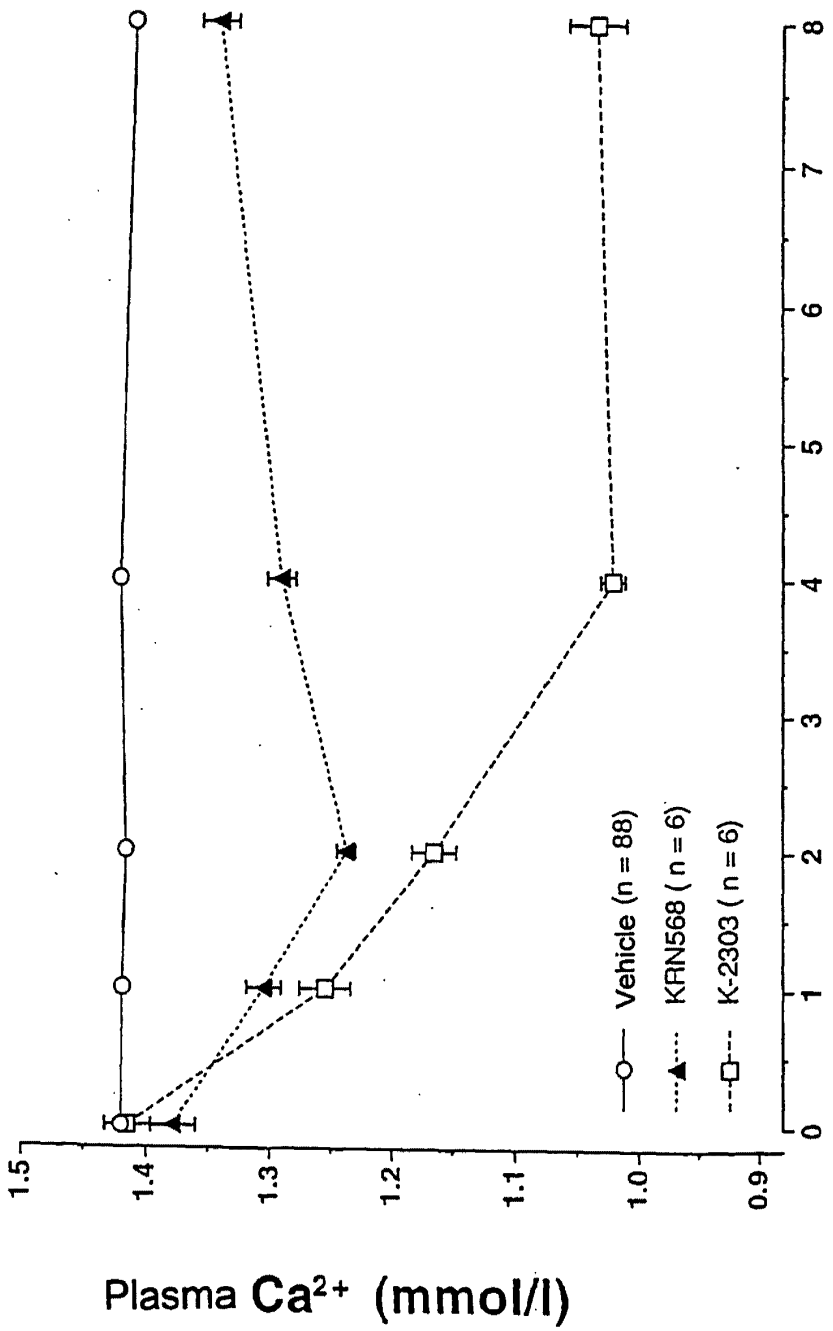

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2303 (n = 6)

Fig. 90

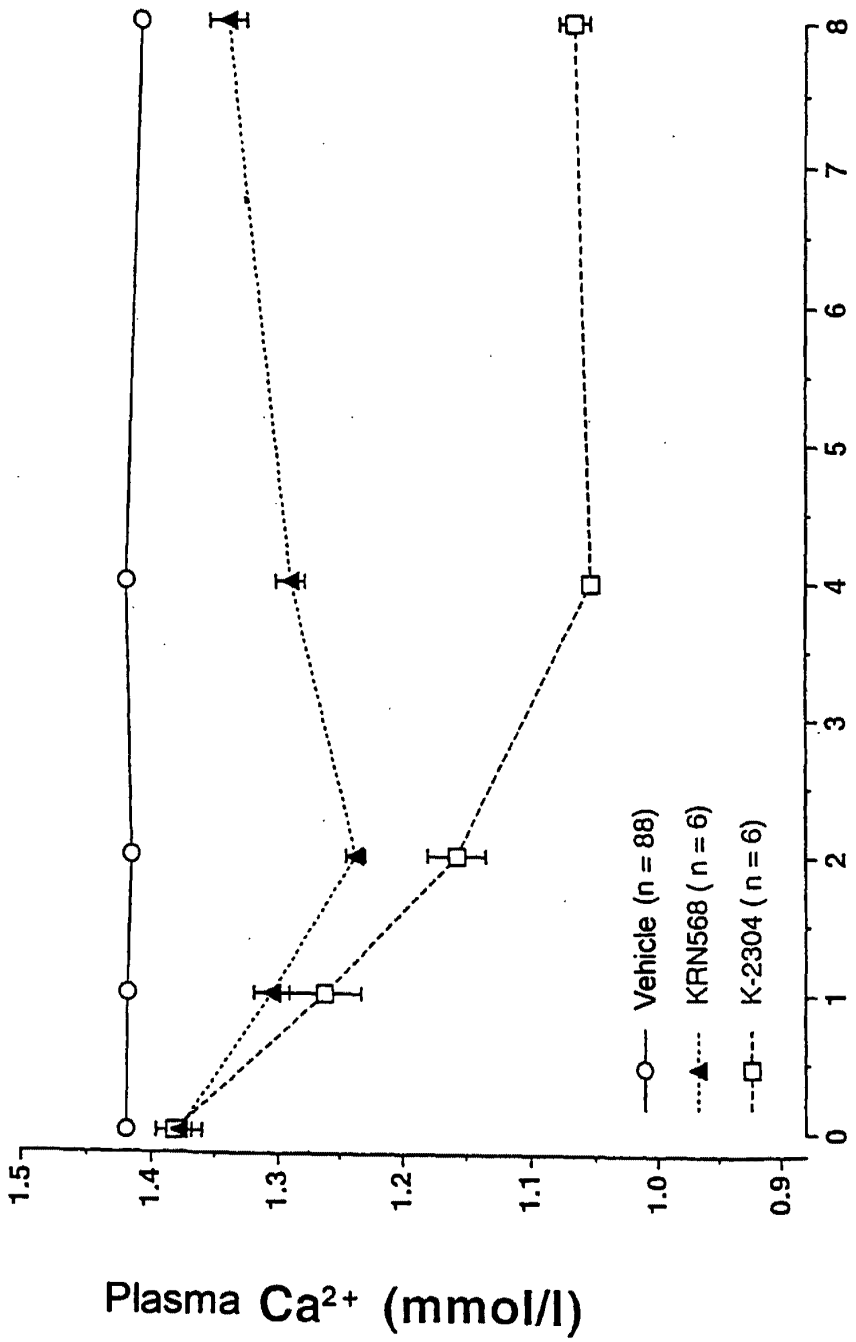

Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8
Time (hr)
Vehicle (n = 88)
KRN568 (n = 6)
K-2304 (n = 6)

Fig. 91

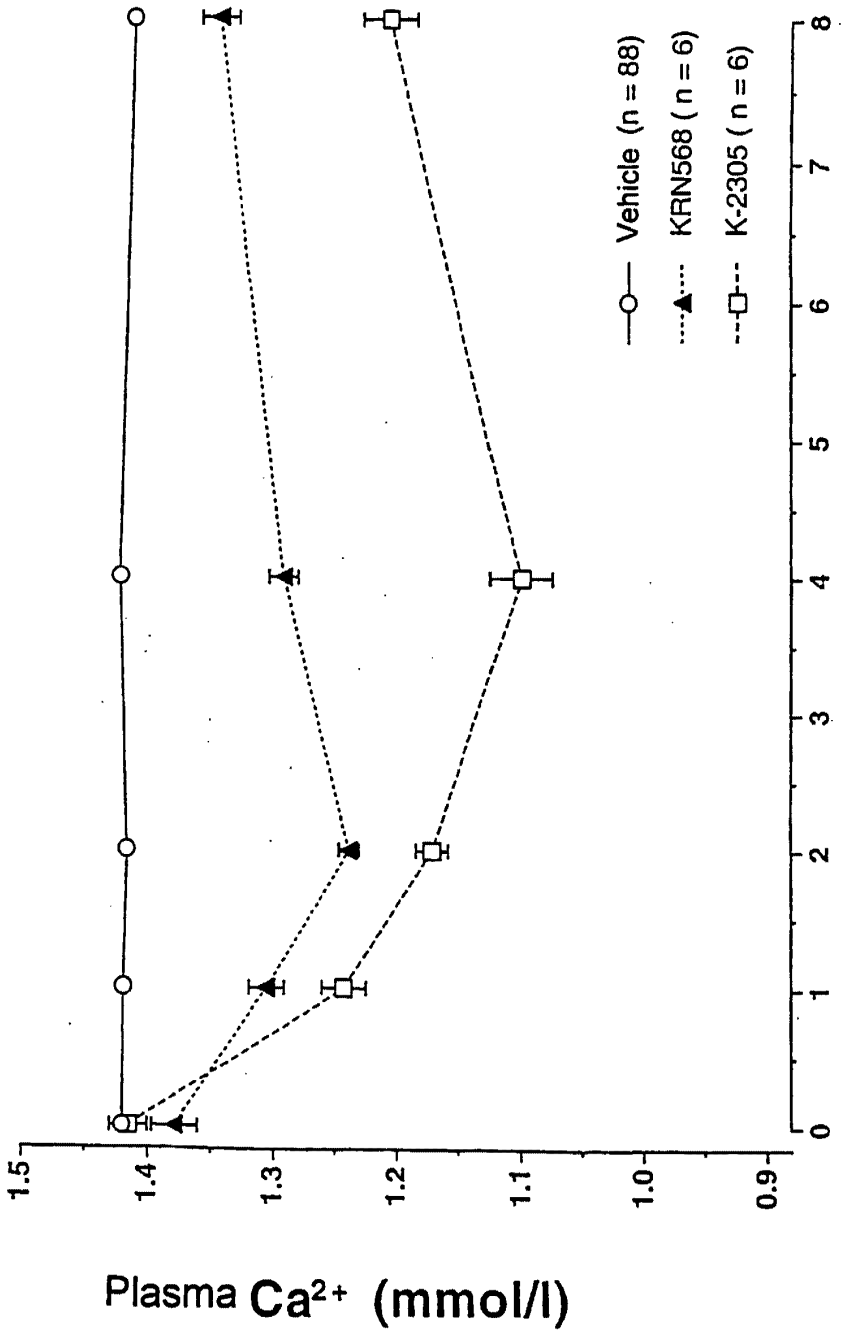

Vehicle (n = 88)
KRN568 (n = 6)
K-2305 (n = 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
1
2
3
4
5
6
7
8

Fig. 92

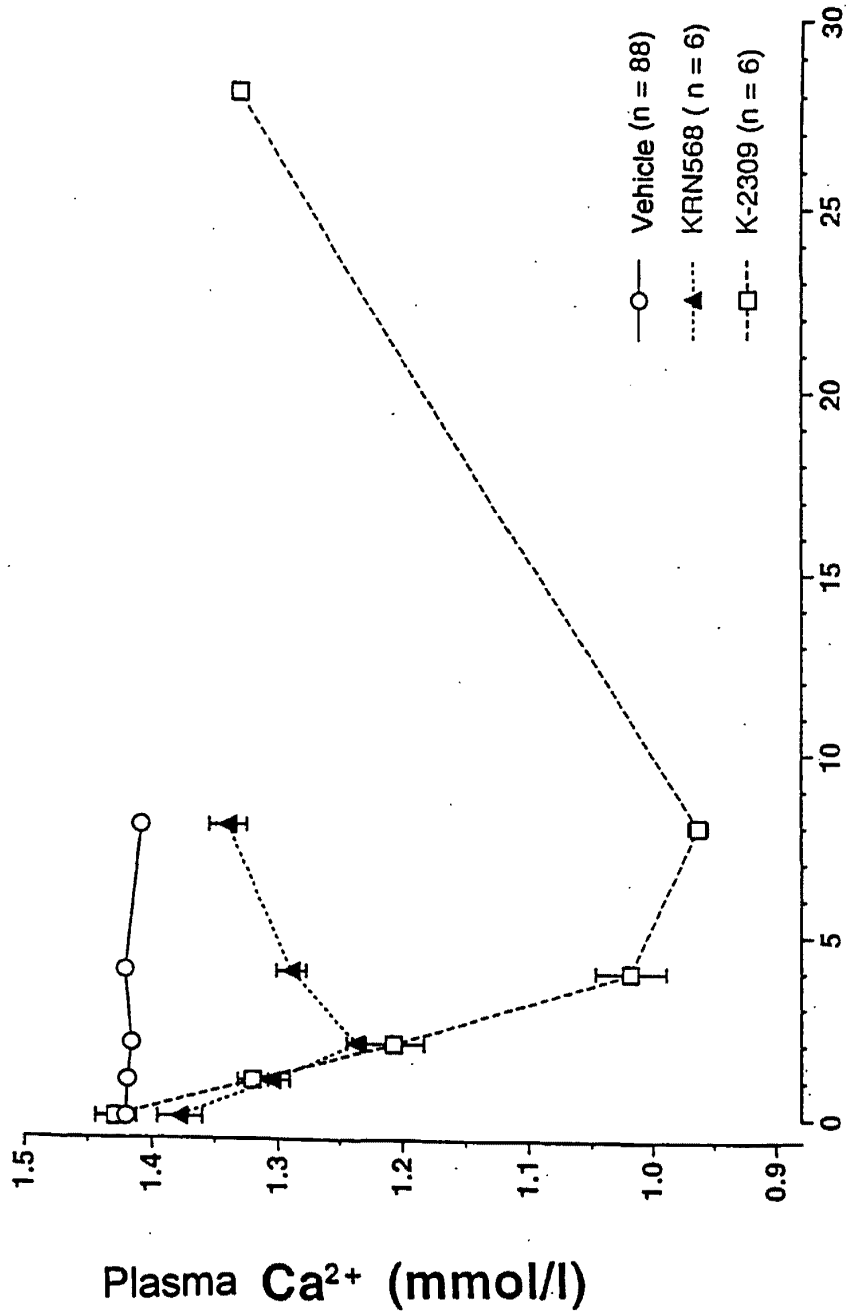

Vehicle (n = 88)
KRN568 (n = 6)
K-2309 (n = 6)
Plasma Ca2+ (mmol/l)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30
Time (hr)

Fig. 93

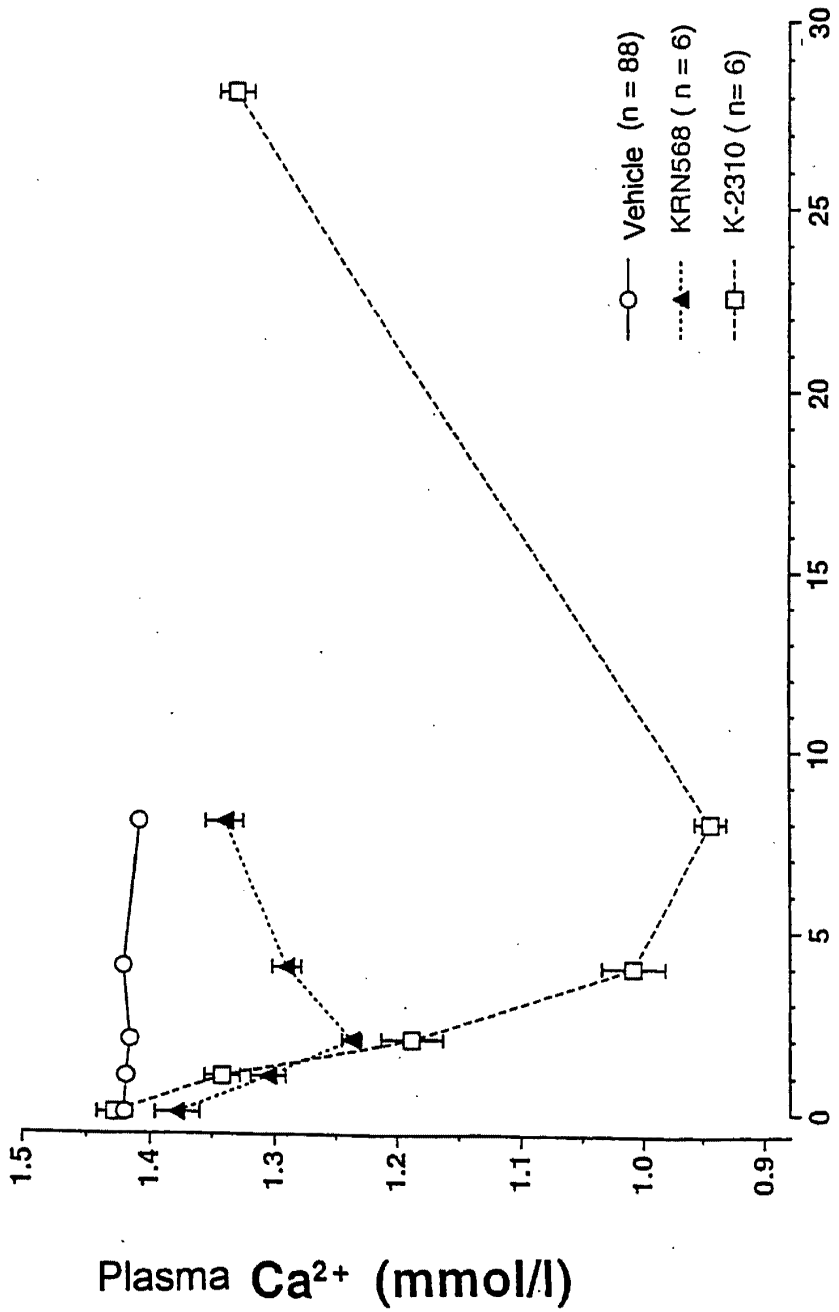

Vehicle (n = 88)
KRN568 (n = 6)
K-2310 (n= 6)
Plasma Ca2+ (mmol/l)
Time (hr)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
5
10
15
20
25
30

Fig. 94

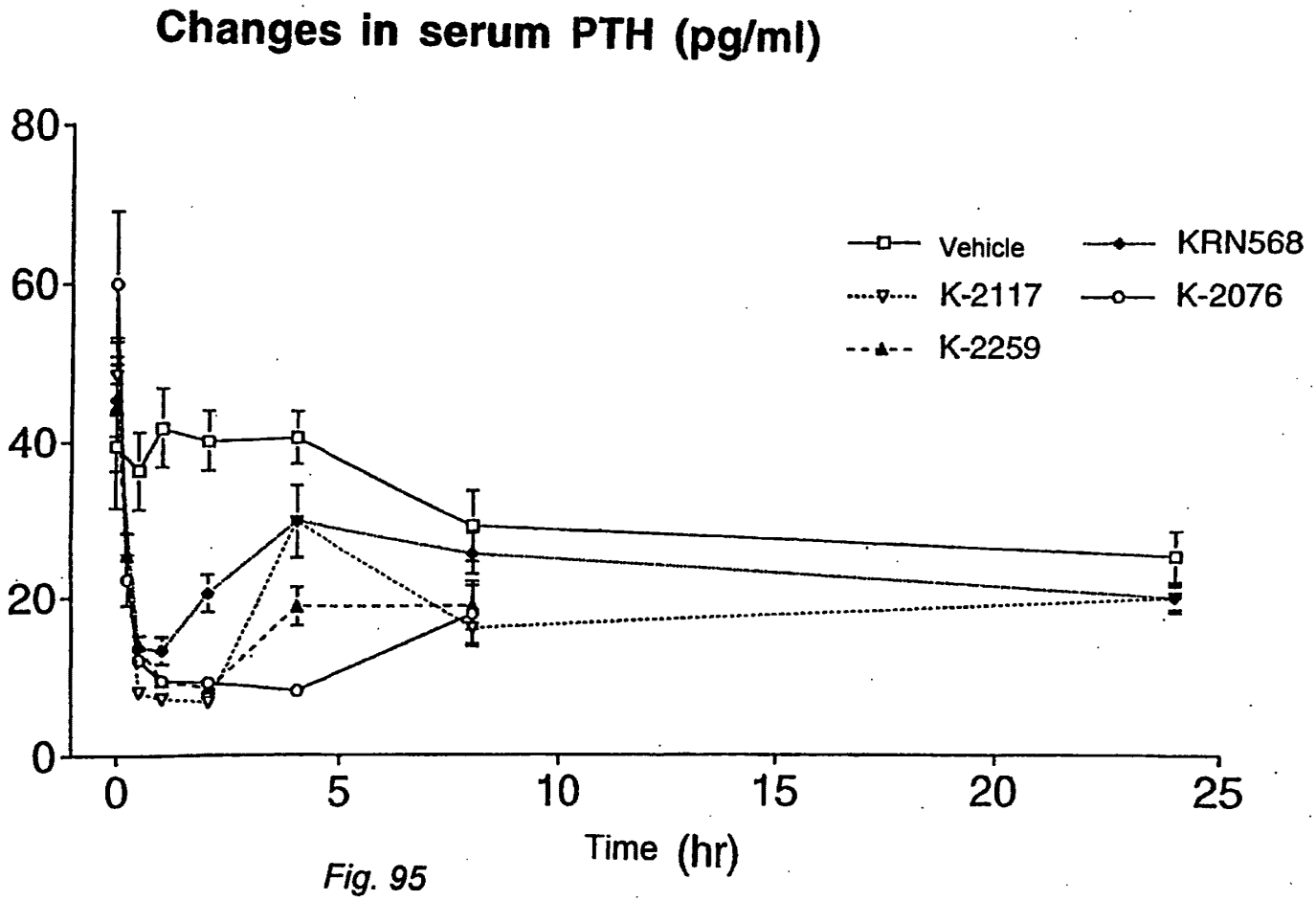

Changes in serum PTH (pg/ml)
80
60
40
20
0
0
5
10
15
20
25
Time (hr)
Vehicle
KRN568
K-2117
K-2076
K-2259

Fig. 95

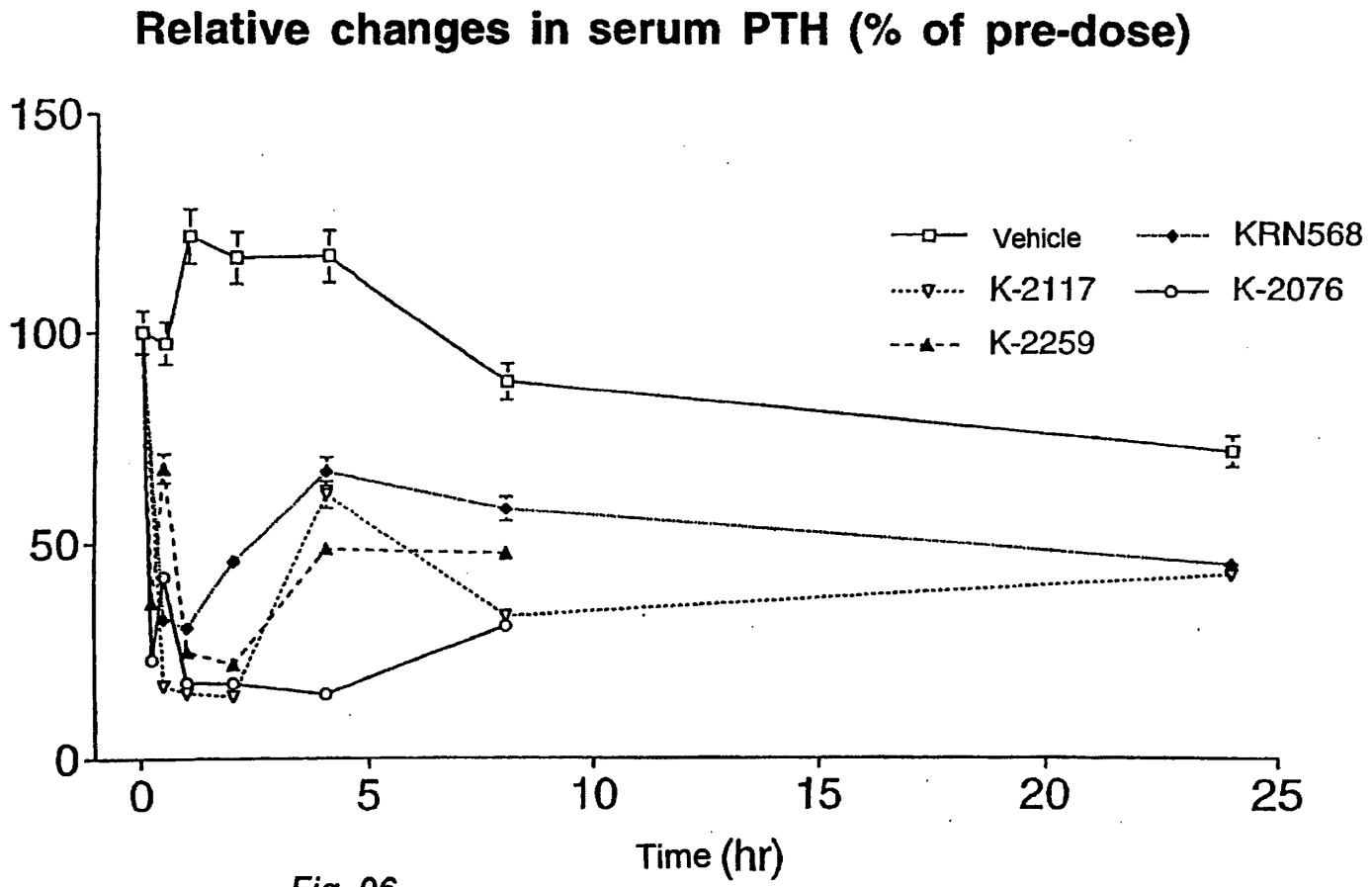

Relative changes in serum PTH (% of pre-dose)
150
100
50
0
0
5
10
15
20
25
Time (hr)
Vehicle
KRN568
K-2117
K-2076
K-2259

Fig. 96

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02358

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 C07C211/30, C07C211/29, C07C211/27, C07C217/14, C07C225/16, C07C237/04, C07C323/23, C07C317/26, C07D209/08,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 C07C1/00-409/44, C07D201/00-521/00, A61K6/00-49/04

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 6-510531, A (NPS Pharmaceuticals Inc.), November 24, 1994 (24. 11. 94) & WO, 93/04373, A1 & AU, 9225889, A & ZA, 9206360, A & CN, 1071333, A & NO, 9400581, A & EP, 657029, A1 & AU, 673500, B	1 - 37 47 - 56
X	WO, 94/18959, A1 (NPS Pharm. Inc.), September 1, 1994 (01. 09. 94) & AU, 937770, A & EP, 637237, A1 & JP, 7506380, A	1 - 37 47 - 56
X	WO, 96/12697, A1 (NPS Pharm. Inc.), May 2, 1996 (02. 05. 96) & AU, 9641957, A & EP, 787122, A1	1 - 37 47 - 56
X	Takano et al. 'A facile route to tetrahydroisoquinoline alkaloids via sulfoxide mediated cyclization', Heterocycles, 35(1)(1977) p. 47-52	1 - 17 19 - 27 29 - 36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
September 29, 1997 (29. 09. 97)	October 21, 1997 (21. 10. 97)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02358

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Riley et al. 'Synthesis and α-adrenolytic activity of chiral N-aralkyl-ß-haloethylamines', J. Pharm. Sci., 65(4) (1976) p. 544-547	1 - 17 19 - 27 29 - 36
X	Chem. Abstr., Vol. 63 (1965) (Columbus, OH, USA), abstract No. 2928b, Wellcome Foundation Ltd. 'Quaternary ammonium compounds', GB 982,572	1 - 17 19 - 27 29 - 36
X	Chem. Abstr., Vol. 60 (1964) (Columbus, OH, USA), abstract No. 11246g, Robert P. Halliday et al. 'Evaluation of certain hypotensive agents. V. Substituted polymethylene diamines', J. Pharm. Sci., 53(1)(1964) p. 19-23	1 - 17 19 - 27 29 - 36
X	Chem. Abstr., Vol. 60 (1964) (Columbus, OH, USA), abstract No. 1692c, Jerry E. Robertson et al. 'Hypotensives. VI. Disubstituted alkylenediamines and related compounds', J. Med. Chem., 6(6) (1963) p. 805-807	1 - 17 19 - 27 29 - 36
X	Chem. Abstr., Vol. 60 (1964) (Columbus, OH, USA), abstract No. 4920f, L. Schusteritz et al. 'Structure and action o piperazine and ethylenediamine derivatives', Arzneimittel-Forsch., 9 (1959), p. 628-633	1 - 17 19 - 27 29 - 36
X	Chem. Abstr., Vol. 53 (1959) (Columbus, OH, USA), abstract No. 12303e, Joseph L. Szabo et al. 'Heterocyclic diamines and salts', US2,876,236	1 - 17 19 - 26 29 - 36
X	Chem. Abstr., Vol. 53 (1959) (Columbus, OH, USA), abstract No. 9251b, Joseph L. Szabo et al. 'Aliphatic diamines and their salts', US2,868,833	1 - 17 19 - 27 29 - 36
X	Chem. Abstr., Vol. 53 (1959) (Columbus, OH, USA), abstract No. 8788d, Roy S. Hauslick et al. Diaralkylenediamine', US2,770,653	1 - 17 19 - 27 29 - 36
X	Chem. Abstr., Vol. 51 (1957) (Columbus, OH, USA), abstract No. 7428i, Lee C. Cheney 'Purification of streptomycin', US2,767,168	1 - 17 19 - 27 29 - 36

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02358

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 38 - 46
because they relate to subject matter not required to be searched by this Authority, namely:
They pertain to methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

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

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02358

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

C07D209/12, C07D209/14, C07D307/91, C07D263/58, C07D311/30, C07D215/36, C07D277/70, C07D281/10, A61K31/40, A61K31/42, A61K31/35, A61K31/34, A61K31/47

Form PCT/ISA/210 (extra sheet) (July 1992)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/937,870	09/10/2004	Glen Gary Lawrence	A-870	1696

22852 7590 04/26/2007

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
31 DAYS	04/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/937,870	LAWRENCE ET AL.	
	Examiner	Art Unit	
	Jagadishwar R. Samala	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-118* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-60 and 78-112 are, drawn to a pharmaceutical composition comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipients, classified in class 424, subclass 9.2.

II. Claims 61-71 are, drawn to a method of making a pharmaceutical composition comprising: forming a granule comprising an effective dosage amount of a calcium receptor-active compound and controlling the particle size of the granule, classified in class 424, subclass 474, 489.

III. Claims 72-77 are, drawn to a method for the treatment of at least one disease chosen from hyperparathyroidism... , comprising administering to a patient, classified in class 424, subclass 488.

IV. Claims 113-118 are, drawn to a method of controlling the dissolution rate of a formulation comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipients, classified in class 424, subclass 464.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions 1 and II are related as product and process of making. The inventions are distinct if either or both of the following can be shown: (1) that the process as

claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case group I is drawn to a pharmaceutical composition comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipients and group II is drawn to a method of making a pharmaceutical composition comprising: forming a granule comprising an effective dosage amount of a calcium receptor-active compound and controlling the particle size of the granule, yet group I, the product can be made by materially process.

3. Inventions I and III (or IV) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case group I is drawn to a pharmaceutical composition comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipients and group III is drawn to a method for the treatment of at least one disease chosen from hyperparathyroidism... , comprising administering to a patient, yet the process for using the product can be practiced with materially different product.

In the event that applicant elects group I, the following election of species is required. This application contains claims directed to the following patentably distinct species of the claimed invention (a) excipients and (b) additive:

(a) excipients (claim 31)

i. microcrystalline cellulose

ii. starch

iii. talc

iv. providone

v. crospovidone

vi. magnesium stearate

vii. colloidal silicon dioxide

viii . sodium dodecyl sulfate

(b) additive (claim 43)

i. glidants

ii. lubricants

iii. adherents

4. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jagadishwar R. Samala whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jagadishwar R Samala
Examiner
Art Unit 1618

sjr

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

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MAY 29 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Glen Lawrence et al.**	Attorney Docket No. **A-870-US-NP**
Application No.: **10/937,870**	Art Unit No.: **1618**
Filed: **09/10/2004**	Examiner: **Jagadishwar R. Samala**
Title: **Rapid Dissolution Formulation of a Calcium Receptor-Active Compound**	

RESPONSE TO RESTRICTION REQUIREMENT

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir/Madame:

This communication is in response to the Office Action mailed April 26, 2007, concerning the above-referenced patent application.

REMARKS

A response to the Office Action dated April 26, 2007, is filed herewith.

In the Official Action dated April 26, 2007, the Examiner required restriction to one of four inventions. The Action further required Applicants to elect a single disclosed species from within the group.

Applicants hereby provisionally elect the invention of Group I, claims 1-60 and 78-112 for examination, with traverse. The traverse is based on the fact that for at least some of the groups set forth in the Restriction Requirement, no search is required beyond that for Group I, and so it is submitted that to examine the groups together would not be unduly burdensome. Applicants provisionally elect the following species:

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper (along with any referred to as being attached or enclosed) (2 pages total) is being facsimile transmitted to the United States Patent and Trademark Office, 571-273-8300, on the date shown below:

May 29, 2007 — Julie M. Balot
Date

(i) microcrystalline cellulose from the (a) excipients group (claim 31), and (ii) lubricants from (b) additive group (claim 43) with traverse. It is submitted that to examine the species together would not be unduly burdensome.

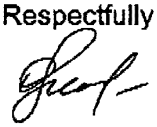
CONCLUSION

The foregoing elections and remarks are believed to constitute a complete response to the restriction requirement of April 26, 2007. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if the Examiner has any questions or would like to discuss any issues related to this application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 01-0523.

Respectfully submitted,



Dated: May 29, 2007.

Olga Mekhovich
Attorney Name, Reg. No. L0066
Attorney for Applicants
AMGEN INC.
1120 Veterans Boulevard
South San Francisco, CA 94080
Phone: (650) 244-2245
Fax: (650) 837-9422

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2004

Application or Docket Number: 10937870

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	118	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	118 minus 20=	* 98
INDEPENDENT CLAIMS	11 minus 3 =	* 8
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	395.00	OR	BASIC FEE	790.00
X$ 9=		OR	X$18=	116
X44=		OR	X88=	704
+150=		OR	+300=	
TOTAL		OR	TOTAL	610

CLAIMS AS AMENDED - PART II

AMENDMENT A — 5-29-07

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 118	Minus	** 118	= 0
Independent	* 11	Minus	*** 11	= 0
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X44=		OR	X88=	
+150=		OR	+300=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X44=		OR	X88=	
+150=		OR	+300=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X44=		OR	X88=	
+150=		OR	+300=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Glen Lawrence et al.	Docket No.:	A-870-US-NP
Serial No.:	10/937,870	Group Art Unit No.:	1618
Filed:	September 10, 2004	Examiner:	Jagadishwar R. Samala
For:	RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND		

STATEMENT UNDER 37 C.F.R. 3.73(b)

Amgen Inc. (hereinafter "Amgen"), a corporation of the State of Delaware having a place of business at One Amgen Center Drive, Thousand Oaks, California, 91320, is the assignee of the entire right, title, and interest in the above-identified U.S. patent application. A chain of title from the inventors of the above-identified application to Amgen Inc. is shown below:

1. From: Inventor Tzuchi R. Ju To: Amgen Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 017562, Frame 0756 on May 2, 2006.

2. From: Inventors Lawrence, Alvarez and Lin To: Amgen Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 016361, Frame 0486 on March 8, 2005.

The undersigned, whose title is supplied below, is empowered to sign this statement on behalf of Amgen.

REVOCATION OF PREVIOUS POWER OF ATTORNEY AND NEW POWER OF ATTORNEY BY ASSIGNEE

Amgen hereby revokes all previous powers of attorney given in the above-identified application and hereby appoints the registered practitioners at Customer Number 30174 to prosecute this application, to make and to transact all business in the Patent and Trademark Office connected therewith.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper (along with any referred to as being attached or enclosed) (2 pages total) is being facsimile transmitted to the United States Patent and Trademark Office, (571-273-8300) on the date shown below:

6-4-2007 Date

Julie M. Balot

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PATENT APPLICATION

REQUEST FOR CHANGE OF CORRESPONDENCE ADDRESS

Please send all future correspondence and direct telephone calls to Customer Number 30174.

Respectfully submitted,

Date May 29, 2007

By Stuart L. Watt
Stuart L. Watt, Vice President, Law
Amgen Inc., Assignee

PAGE 2/2 * RCVD AT 6/4/2007 3:50:48 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-3/16 * DNIS:2738300 * CSID:6508379422 * DURATION (mm-ss):00-40

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/937,870	09/10/2004	Glen Gary Lawrence	A-870

CONFIRMATION NO. 1696

OC000000024384749

22852
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

Date Mailed: 06/15/2007

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/04/2007.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199
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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/937,870	09/10/2004	Glen Gary Lawrence	A-870-US-NP

CONFIRMATION NO. 1696

30174
AMGEN INC.
1120 VETERANS BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

OC000000024384876

Date Mailed: 06/15/2007

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/04/2007.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199
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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	2	"6495165".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/13 17:07
S2	2	"6432656".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:38
S3	2	"6399100".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:39
S4	2	"6387404".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:42
S5	2	"6363231".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:43
S6	2	"6342532".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:46
S7	2	"6313146".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:47
S8	2	"6277788".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:47

EAST Search History

S9	2	"6228807".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:48
S10	2	"6172091".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/23 11:48
S11	2	"6031003".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 18:24
S12	23	(calcimimetic and calcilytic adj compound)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 10:26
S13	212	(calcimimetic calcilytic)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 11:19
S14	282830	(calcimimetic calcilyticand granules)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 10:26
S15	144	(calcimimetic calcilytic and methylcellulose)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 11:37
S16	138	(calcimimetic calcilytic and microcrystallinecellulose)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:10

EAST Search History

S17	0	(microcrystallinecellulose and calciun adj receptors)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:11
S18	32	(microcrystallinecellulose)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:16
S19	23	S14 and S18	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:14
S20	0	S13 and S18	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:15
S21	7645	(hyperparathyroidism hyperphosphonia hypercalcemia)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:16
S22	0	S18 and S21	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:16
S23	43414	(microcrystalline adj cellulose)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:06
S24	1370	S21 and S23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:25

EAST Search History

S25	8	S13 and S24	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:18
S26	699	(calcium adj receptors)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:19
S27	35	S23 and S26	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 12:19
S28	414	S24 and @py<"2003"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:01
S29	45943	(microcrystalline adj cellulose avicel)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:27
S30	14	S13 and S29	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:10
S31	35	S26 and S29	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:16
S32	21846	S14 and S23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:16

EAST Search History

S33	9	S32 and calcilytic	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:17
S34	8	S32 and (calcimimetic)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:17
S35	14	S13 and S29	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:17
S36	7	S13 and avicel	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:20
S37	1389	S21 and S29	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:27
S38	422	S37 and @py<"2003"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 17:50
S39	2	"5126145".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:52
S40	2	"5981599".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 13:56

EAST Search History

S41	2	"6001884".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 14:14
S42	2	"6011068".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 14:15
S43	2	"6172091".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 14:28
S44	2	"6211244".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 14:31
S45	2	"6228807".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 14:31
S46	2	"6277788".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 14:32
S47	2	"6313146".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 13:18
S48	2	"6342532".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 15:16

EAST Search History

S49	2	"6363231".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 15:17
S50	2	"6387404".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 15:32
S51	2	"6399100".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 15:34
S52	2	"6495165".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 15:48
S53	2	"20030035836"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 15:48
S54	56	(cinacalcet)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 17:51
S55	2	WO-9511221-$.did.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 18:26
S56	2	WO-9912524-$.did.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 18:27

EAST Search History

S57	2	WO-9612697-$.did.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/16 18:27
S58	45	(cinacalcet and calcium)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 13:20
S59	0	S58 and @py<"2003"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 13:19
S60	6014	(cinacalcet and hyperparathyroidism hyperphosphonia hypercalcemia)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 13:43
S61	2266	S60 and @py<"2003"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 13:33
S62	55	S61 and (calcium adj receptor)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 13:22
S63	56	(cinacalcet)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 14:17
S64	22	(cinacalcet and calcimimetics)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/07/17 14:19

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/937,870	09/10/2004	Glen Gary Lawrence	A-870-US-NP	1696

30174 7590 07/23/2007
AMGEN INC.
1120 VETERANS BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
07/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/937,870	LAWRENCE ET AL.	
	Examiner	Art Unit	
	Jagadishwar R. Samala	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,39,43,46,47,52-60,78-80,83-97 and 99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,39,43,46,47,52-60,78-80,83-97 and 99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/06/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Restriction Requirement

1. Acknowledgement is made of Applicant's election (with traverse) of Group I claims 1-60 and 78-122, and the species (microcrystalline cellulose and lubricant), in a response filed on May 29, 2007. Applicants traverse the restriction asserting that at least some of the groups set forth in the restriction requirement should be included in group I. Secondly, applicants traverse the requirement to elect a species for search purposes.

The Examiner respectfully disagrees with the Applicants because the composition and method of making, method for treatment and method of controlling the dissolution rate differ materially in elements and from each other and are therefore capable of supporting their own patents. Nevertheless, Examiner may reconsider to rejoin the method claims commensurate in scope with the composition claims when and if the case is found to be in condition for allowance provided those method claims are free of 35 U.S.C. § 112 first and second paragraph issues (including written description, reach-through claims language and/or scope of enablement issues).

Applicants reserve their right to file a divisional application on the non-elected subject matter.

Claims 1-60 and 78-112 are pending. Claims 61-77 and 113-118 are withdrawn. Claims 1-31, 39, 43, 46-47, 52-60, 78-80, 83-97, and 99 are presented for examination and claims 32-38, 40-42, 44-45, 48-51, 81-82, 98, 100-112 are non-elected claims and are withdrawn from consideration.

Information of Disclosure Statement

2. Applicant's Information Disclosure Statement (IDS) filed on September 06, 2005 has been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-31, 39, 43, 46-47, 52-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 and 2 are drawn to a pharmaceutical composition comprising an effective dosage amount of a "calcium receptor-active compound" wherein the calcium receptor-active compound is chosen from calcimimetic compounds and calcilytic compounds. While the examiner acknowledges that the term "calcium receptor-active compound" is mentioned in the instant specification, the term is not defined by the instant specification in a clear and concise manner. The specification only adequately discloses a very limited number of species for this group such as cinacalcet HCl and cinccalcet methanesulfonate. However these are not considered to be representative species for the wide variation of chemical compounds within "calcium receptor-active compound" which may include ionomimetics, ionolytics , bisphosphonate

compounds. As such, the disclosure of the instant specification is not sufficient to support the generic concept of "calcium receptor-active compound" and requires further clarification.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-5 and 7-11, 18, are rejected under 35 U.S.C. 102(b) as being anticipated by Nemeth et al. (US 6,031,003).

With respect to claims 1-5 and 7-11, Nemeth discloses pharmaceutical composition and use of molecules able to modulate the activity of an inorganic ion receptor, preferably a calcium receptor (see col 1, lines 26-29). And also, the inorganic ion receptor-modulating agents include ionomimetics, ionolyitcs, Calcimimetics, and Calcilytics. Preferably, Calcimimetics are ionomimetics, which affect one or more calcium receptor activities and bind to a calcium receptor (see col. 5, line 48-56). Further, the molecule is a substituted R-phenypropyl-α-phenethylamine derivative, or a substituted R-benzyl-α-phenethylamine derivate, having the structure as recited in claim 4 (see col 8, line 21-40). And also, the molecule calcimimetic or calcilytic having an EC_{50} or IC_{50} at a calcium receptor of less than or equal to 5 μM, preferably less than or equal to 1 μM, 100 nmolar, 10 nmolar, or 1 nmolar (see col 8, lines 58-65). And also, the agents can be formulated as pharmaceutically acceptable salts such as hydrochlorides, acetate, citrate, methanesulfonate, ethanesulfonate and the like (see col, 62, lines 28-32). And

also, to facilitate administration of the agent, composition includes carriers and excipients such as calcium phosphate, various sugars, cellulose derivatives, vegetable oils, and physiologically compatible solvents (see col, 62, lines 47-53). And for oral administration, the agents are formulated into conventional oral administration dosage forms such as capsules, tablets, and liquid preparations (see col 63, lines 8-10).

With respect to claims 1 and 7-11, it is the examiner's position that, inherently, the composition advanced by Nemeth provides pharmaceutically acceptable salts of various concentrations to facilitate the pharmacological use by altering the physical characteristic of the agent without preventing it from exerting its physiological effect. Since the essential elements of the Nemeth composition are identical to the instant compositions (that is, excipients like cellulose derivatives, starch, oral dosage forms such as capsules, tablets and further modulation of calcium receptor activity can be used to treat diseases such as primary hyperparathyroidism and secondary hyperparathyroidism0, the composition would inherently have the same physiochemical properties (e.g. dissolution profile) as the composition set forth in the instant application. As such, it is the examiner's position that the composition advanced by Nemeth anticipates the composition enumerated in the instant claim set.

3. Claims 12, 23-29 are rejected under 35 U.S.C. 102(b) as being anticipated by William G. Goodman et al. (J. Am: Soc. Nephrology 13, 1017-1024, 2002).

Goodman discloses calcimimetic agents such as AMG 073 agent (cinacalcet HCl) for lowering the plasma parathyroid hormone levels in hemodialysis patients suffering from secondary hyperparathyroidism due to ESRD (see abstract). And also, repeated daily orally

administered doses of the calcimimetic agent AMG 073 effectively reduce plasma PTH levels, decrease serum phosphorus concentrations, and lower the calcium-phosphorus ion product in hemodialysis patients with secondary hyperparathyroidism (see page 1023). The bioavailability of AMG 073 after oral administration is greater and it exhibits a more consistent pharmacokinetic profile. Cinacalcet HCl has demonstrated efficacy in controlling the hpercalcemia of severe primary HPT and in reducing parathyroid hormone levels in patient with secondary HPT Since all critical elements as required by instant claims are taught by the cited reference and claims are anticipated.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-31, 39, 43, 46-47, 52-60, 78-80, 83-97 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over William G. Goodman et al. (J. Am. Soc. Nephrology 13, 1017-1024, 2002) in view of Ault et al (US 2002/0123459) or Black et al. (US 2001/0051636) or Krumhar et al. (US 6,447,809).

Goodman discloses as described above.

Goodman meets the claim limitations as described above but fails in include the granules within the composition comprising microcrystalline cellulose, a lubricant, and a color coating materials.

However, it would have been obvious to one of ordinary skill in the art at that time of the invention was made to incorporate additional additives such as microcrystalline cellulose, a lubricant, a color coating materials to increase the therapeutic efficacy when Goodman is taken in view of Ault or Black and Krumhar together teach a enhancement of therapeutic efficacy when a combination of pharmacologically active agents, and to methods of treating and/or preventing diseases particularly osteomalacia, hypercalcemia of malignancy, osteopenia due to bone metastases and hyperparathyroidism (all of these conditions are characterized by bone loss, resulting from an imbalance between the degradation of bone resorption and the formation of new healthy bone) is used to increase the calcium receptor-activity where calcimimetic compounds has undergone thru very same mechanism for the treatment of primary and secondary hyperparathyroidism.

7. Ault discloses a pharmaceutical composition suitable for the oral delivery of calcitonin in an effective amount commonly employed in the treatment of e.g. paget's disease, hypercalcemia and postmenopausal osteoporosis (see abstract and 0023). And composition additionally

comprises excipients, diluents such as microcrystalline cellulose, a lubricant such as magnesium stearate, a colorant, a humectants, surfactant or any combination thereof (see 0048).

Black discloses a pharmaceutical compositions comprising administering a pharmaceutically active agent, with a bisphosphonate in the treatment of paget's disease, osteohalisteresis, osteomalacia hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal diseases, and hyperparathyroidism (see 0001). And also, the compounds are preferably employed in the form of tablets, granules, pills, powders lozenges, sachets elixirs, emulsions, solutions and soft and hard gelatin capsules. (see 0110). The composition further includes suitable carriers, lubricants, diluents, and excipients such as microcrystalline cellulose, talc, magnesium stearate and thereof (see 0111). And also, compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to 500 mg of the active ingredient (see 0113).

Krumhar discloses a composition for use as a dietary supplements that, when ingested, will reduce bone turnover rate by inhibiting bone resorption while increasing the retention of calcium, phosphorus, and potassium in the human body (see col 4, lines 30-42). And further, the composition is used for treatment of osteoporosis, paget's disease, and hyperparathyroidism-conditions of high bone turnover (see col 10, lines 26-30). And further, the composition comprising active ingredient are preferably employed in the form of tablets containing additional excipients and additives, diluents and disintegrant such as microcrystalline cellulose (disintegrants are substance that facilitate the breakup or disintegration of tablet after administration, see col 9, line 23-29), a lubricant such as talc, magnesium stearate, calcium

stearate, stearic acid and hydrogenated vegetable oils (see col 8, lines 56-64), coloring agents (any of the approved certified water-soluble FD&C dyes, mixtures thereof, see c0l 9, lines 8-15).

When these references are taken together, one would have been motivated to extend Goodman's teaching to add additional additives such as microcrystalline cellulose, a lubricant, a color coating materials to maximize therapeutic efficacy. As suggested by cited references, one would have reasonably expected successful addition of secondary ingredients (such as microcrystalline cellulose, a lubricant, a color coating materials) because the effectiveness, extra benefits (i.e., bone resorption) and safety are already well proven and are well suggested by latter references cited.

One would have been motivated to do so, with reasonable expectation of success because it is always desirable to have extended therapeutic modalities to improve patient's compliance by enhancing patient satisfaction and increasing the selection option. The techniques and skills required for making such substitution is conventional knowledge or well within the skills of ordinary artisan as evidenced by these references cited.

The daily dosages are well suggested and minor variations (dissolution profile) can be easily titrated and obtained in order to determine best outcomes, and it is considered to be routine practice especially having dosage suggestions by Goodman work. Said difference would not render the claimed invention patentably distinct, it is obvious because the modification is well within the skilled level of the artisan and considered to be a routine optimization commonly practiced in the art, as evidenced by cited references.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share

common utilities, and pertinent to the problem which applicant concerns about. MPEP 2141.01 (a).

Conclusion

1. No claims are allowed at this time.

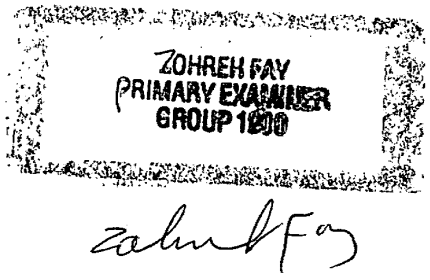
2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jagadishwar R. Samala whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jagadishwar R Samala
Examiner
Art Unit 1618

sjr



Modified Form PTO-1449	Atty. Docket No. A-870 (US)	Serial No. 10/937.870
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	Applicant GLEN LAWRENCE ET AL.	
	Filing Date Sept. 10, 2004	Group 1614

U.S. PATENT DOCUMENTS

EXAMINER'S INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
/JS/	A1	5,126,145	6/30/1992	Evenstad et al.			
	A2	5,981,599	11/9/1999	Moe et al.			
	A3	6,001,884	12/14/1999	Nemeth et al.			
	A4	6,011,068	1/4/2000	Nemeth et al.			
	A5	6,031,003	2/29/2000	Nemeth et al.			
	A6	6,172,091	1/9/2001	Cohen et al.			
	A7	6,211,244	4/3/2001	Van Wagenen et al.			
	A8	6,228,807	5/8/2001	Kuchikata et al.			
	A9	6,277,788	8/21/2001	Wright			
	A10	6,313,146	11/6/2001	Van Wagenen et al.			
	A11	6,342,532	1/29/2002	Moe et al.			
	A12	6,363,231	3/26/2002	Manzer et al.			
	A13	6,387,404	5/14/2002	Oshlack et al.			
	A14	6,399,100	6/4/2002	Clancy et al.			
	A15	6,432,656	8/13/2002	Del Mar et al.			
	A16	6,495,165	12/17/2002	Thosar et al.			
	A17	2002/0015735	2/7/2002	Hedden et al.			
	A18	2002/0107406	8/8/2002	Sakai et al.			
	A19	2003/0035836	2/20/2003	Shanghvi et al.			
/JS/	A20	2003/0054041	3/20/2003	Lemmens et al.			

EXAMINER: /Jagadishwar Samala/	Date Considered: (07/18/2007)

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Modified Form PTO-1449	Atty. Docket No. A-870 (US)	Serial No. 10/937,870
LIST OF REFERENCES CITED BY APPLICANT	Applicant GLEN LAWRENCE ET AL.	
(Use several sheets if necessary)	Filing Date Sept. 10, 2004	Group 1614

FOREIGN PATENT DOCUMENTS

EXAMINER' INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
/JS/	B1	WO 93/04373	3/4/1993	PCT				
	B2	WO 94/18959	9/1/1994	PCT				
	B3	WO 95/11221	4/27/1995	PCT				
	B4	WO 96/12697	5/2/1996	PCT				
	B5	WO 97/41090	11/6/1997	PCT				
↓	B6	WO 01/34562	5/17/2001	PCT				
/JS/	B7	EP 0 933 354	8/4/1999	EUROPE				

EXAMINER:	Date Considered:
/Jagadishwar Samala/	(07/18/2007)

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

A-25b (Rev. 07/01/03)

Modified Form PTO-1449	Atty. Docket No. A-870 (US)	Serial No. 10/937,870
LIST OF REFERENCES CITED BY APPLICANT	Applicant GLEN LAWRENCE ET AL.	
(Use several sheets if necessary)	Filing Date Sept. 10, 2004	Group 1614

EXAMINER'S INITIALS		**OTHER DOCUMENTS (Including Publisher, Author, Title, Date, Pertinent Pages, Etc.)**
/JS/	C1	Amgen News Release, Internet Article: "Amgen Submitted New Drug Application for Cinecalcet HC1", XP002313388, URL: http://www.amgen.com/news/news03/pressRelease030908a.pdf, September 8, 2003, 2 pages.
	C2	Berge, Stephen M., et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, Vol. 66, No. 1, pp. 1-19, January 1977
	C3	Drugs in R&D, "Cinecalcet: AMG 073, Calcimimetics – Amgen/NPS Pharmaceuticals, KRN 1493, NPS 1493," Vol. 4, No. 6, pp 349-351, 2003
	C4	Goodman, William G., et al., "The Calcimimetic Agent AMG 073 Lowers Plasma Parathyroid Hormone Levels in Hemodialysis Patients with Secondary Hyperparathyroidism," *J. Am. Soc. Nephrol*, Vol. 13, pp. 1017-1024, April 2002
	C5	Nemeth, Edward F., et al., "Pharmacodynamics of the Type II Calcimimetic Compound Cinacalcet HCl, *J. Pharmacol. Exp Therapeutics*, Vol. 308, No. 2, pp. 627-635, February 2004
	C6	Pattaragarn, Anirut, et al., "Effect of the Calcimimetic NPS R-467 on Furosemide-Induced Nephrocalcinosis in the Young Rat," *Kidney Internationa*, Vol. 65, pp. 1684-1689, 2004
	C7	U.S. Food and Drug Administration, Internet Article: "FDA Approves First in a New Class of Drugs to Treat Hyperparathyroidism Associated with Renal Failure and in Patients with Parathyroid Cancer, " *FDA Talk Paper*, XP-002313389, http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01282.html), March 8, 2004, 1 page, (retrieved by EPO Searching Authority on 1/11/2005)
	C8	RxList, Inc., Internet Article: "Sensipar (Cinacalcet HCl) Tablets," XP-002313390, www.rxlist.com/cgi/generic3/sensipar.htm), August 12, 2004, 2 pages, (retrieved by EPO Searching Authority on 1/10/2005)
/JS/	C9	NPS Pharmaceuticals, Internet Article: "NPS Drug Development: Product Development Pipeline," XP-002313391, www.npsp.com/drug-development/pipline.php, September 8, 2003, 2 pages, (retrieved by EPO Searching Authority on 1/12/2005)

EXAMINER:	Date Considered:
/Jagadishwar Samala/	(07/18/2007)

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Notice of References Cited	Application/Control No. 10/937,870	Applicant(s)/Patent Under Reexamination LAWRENCE ET AL.	
	Examiner Jagadishwar R. Samala	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,031,003	02-2000	Nemeth et al.	514/579
*	B	US-2002/0123459	09-2002	Ault et al.	514/2
*	C	US-2001/0051636	12-2001	Black et al.	514/320
*	D	US-6,447,809	09-2002	Krumhar et al.	424/602
	E	US-			
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	I	US-			
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	William G. Goodman, Gerald A. Hladik, Stewart A. Turner, Peter W. Blaisdell, David A. Goodkin, Wei Liu, Yousir M. Barri, Raphael M. Cohen and Jack W. Coburn, The Calcimimetic Agent AMG 073 Lowers Plasma parathyroid Hormone levels in Hemodialysis patients with Secondary Hyperparathyroidism, J. Am. Soc. Nephrology, 13, 1017-1024, 2002.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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BIB DATA SHEET

CONFIRMATION NO. 1696

SERIAL NUMBER	FILING or 371(c) DATE / RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/937,870	09/10/2004	514	1618	A-870-US-NP

APPLICANTS

Glen Gary Lawrence, Thousand Oaks, CA;
Francisco J. Alvarez, Newbury Park, CA;
Hung-Ren H. Lin, Oak Park, CA;
Tzuchi R. Ju, Vernon Hills, IL;

**** CONTINUING DATA ***************************

This appln claims benefit of 60/502,219 09/12/2003

**** FOREIGN APPLICATIONS *************************** None

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

11/01/2004

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☒ No	☐ Yes ☒ No	Examiner's Signature	☐ Initials SJ.	CA	0	118	11

ADDRESS

AMGEN INC.
1120 VETERANS BOULEVARD
SOUTH SAN FRANCISCO, CA 94080
UNITED STATES

TITLE

Rapid dissolution formulation of a calcium receptor-active compound

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
7420	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/937,870	LAWRENCE ET AL.
Examiner	**Art Unit**
Jagadishwar R. Samala	1618

✓	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Claim		Date								
Final	Original	07/17/07								
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/937,870	LAWRENCE ET AL.
Examiner	**Art Unit**
Jagadishwar R. Samala	1618

SEARCHED			
Class	Subclass	Date	Examiner
514	2 307 320	7/17/2007	SJ
514	167 168 456	7/17/2007	SJ

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
East Search Report Enclosed	7/17/2007	SJ
Inventors name search	7/17/2007	SJ

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	**Glen Lawrence et al.**	Docket No.:	**A-870-US-NP**
Serial No.:	**10/937,870**	Group Art Unit No.:	**1618**
Filed:	**09/10/2004**	Examiner:	**Jagadishwar R. Samala**

For: **Rapid Dissolution Formulation of a Calcium Receptor-Active Compound**

RESPONSE TO OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

In response to the Office Action mailed July 23, 2007, Applicants request a two month extension of time in the shortened statutory period of response and request that the application be amended as follows. A Petition for Extension of Time (in duplicate) is hereby submitted.

Amendments to the claims are reflected in the listing of claims beginning on page 2 of this paper.

Remarks begin on page 13 of this paper.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper (along with any referred to as being attached or enclosed) (16 pages total) is being facsimile transmitted to the United States Patent and Trademark Office, 571.273.8300, on the date shown below:

December 21, 2007
Date

Julie M. Balot

Atny. Docket No. A-870-US-NP

IN THE CLAIMS

Claims 1-60 and 78-112 are pending. Claims 61-77 and 113-118 are withdrawn. Claims 1-31, 39, 43, 46-47, 52-60, 78-80, 83-97 and 99 are presented for examination. Claims 1-31, 39, 43, 46-47, 52-60, 78-80, 83-97 and 99 are rejected.

Please enter the following listing of claims, which will replace all prior versions, and listings, of claims in the application:

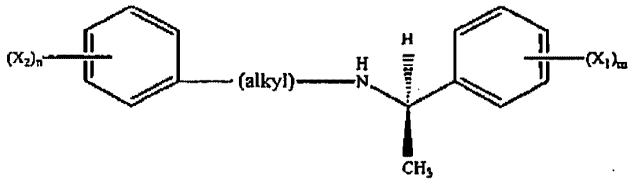
Listing of Claims

1. (Currently Amended) A pharmaceutical composition comprising an effective dosage amount of a calcimimetic compound or a calcilytic compound and at least one pharmaceutically acceptable excipient,

wherein at least one dosage unit of the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the ~~calcium receptor active~~ calcimimetic compound or the calcilytic compound being released from the composition no later than about 30 minutes from the start of the test.

2. (Canceled)

3. (Currently Amended) The composition according to Claim 1 ~~2~~, wherein the calcimimetic compounds and calcilytic compounds are chosen from compounds of formula (I) and pharmaceutically acceptable salts and forms thereof



(I)

wherein:

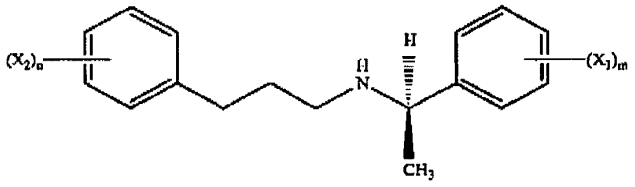
X_1 and X_2, which may be identical or different, are each a radical chosen from CH_3, CH_3O, CH_3CH_2O, Br, Cl, F, CF_3, CHF_2, CH_2F, CF_3O, CH_3S, OH, CH_2OH, $CONH_2$, CN, NO_2, CH_3CH_2, propyl, isopropyl, butyl, isobutyl, t-butyl, acetoxy, and acetyl radicals, or two of X_1 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical, or two of X_2 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical; provided that X_2 is not a 3-t-butyl radical;

n ranges from 0 to 5;

m ranges from 1 to 5; and

the alkyl radical is chosen from C1-C3 alkyl radicals, which are optionally substituted with at least one group chosen from saturated and unsaturated, linear, branched, and cyclic C1-C9 alkyl groups, dihydroindolyl and thiodihydroindolyl groups, and 2-, 3-, and 4-piperid(in)yl groups; and the stereoisomers thereof.

4. (Original) The composition according to Claim 3, wherein the calcimimetic compounds and calcilytic compounds are chosen from compounds of formula (II) and pharmaceutically acceptable salts and forms thereof



(II)

wherein:

X_1 and X_2, which may be identical or different, are each a radical chosen from CH_3, CH_3O, CH_3CH_2O, Br, Cl, F, CF_3, CHF_2, CH_2F, CF_3O, CH_3S, OH, CH_2OH, $CONH_2$, CN, NO_2, CH_3CH_2, propyl, isopropyl, butyl, isobutyl, t-butyl, acetoxy, and acetyl radicals, or two of X_1 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical, or two of X_2 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical; provided that X_2 is not a 3-t-butyl radical;

n ranges from 0 to 5; and
m ranges from 1 to 5.

5. (Original) The composition according to Claim 4, wherein the pharmaceutically acceptable salts and forms thereof are chosen from salts of hydrochloric acid and salts of methanesulfonic acid.

6. (Original) The composition according to Claim 4, wherein the calcimimetic compounds are chosen from cinacalcet, cinacalcet HCl, and cinacalcet methanesulfonate.

7. (Original) The composition according to Claim 1, wherein the dissolution profile comprises from about 70% to about 110% of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

8. (Original) The composition according to Claim 7, wherein the dissolution profile comprises at least about 75% of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

9. (Original) The composition according to Claim 6, wherein the dissolution profile comprises from about 70% to about 110% of the target amount of the cinacalcet HCl being released from the composition no later than about 30 minutes from the start of the test.

10. (Original) The composition according to Claim 9, wherein the dissolution profile comprises at least about 75% of the target amount of the cinacalcet HCl being released from the composition no later than about 30 minutes from the start of the test.

11. (Original) The composition according to Claim 6, wherein the cinacalcet HCl and cinacalcet methanesulfonate are in a form chosen from amorphous powders, crystalline particles and mixtures thereof.

Atny. Docket No. A-870-US-NP

12. (Currently Amended) The composition according to Claim 1, wherein the ~~calcium receptor-active~~ calcimimetic compound is cinacalcet HCl.

13. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is in a form chosen from needle-shape particles, rod-shape particles, plate-shaped particles, and mixtures of any of the foregoing.

14. (Original) The composition according to Claim 12, wherein the particle D_{50} of the cinacalcet HCl particles is less than or equal to about 50 μm.

15. (Original) The composition according to Claim 12, wherein the cinacalcet HCl particles have a particle D_{50} effective to release from about 70% to about 110% of the target amount of the cinacalcet HCl from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

16. (Original) The composition according to Claim 15, wherein the cinacalcet HCl particles have a particle D_{50} effective to release at least about 75% of the target amount of the cinacalcet HCl from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

17. (Original) The composition according to Claim 1, wherein the composition is in the form of granules.

18. (Original) The composition according to Claim 1, wherein the composition is in a form chosen from tablets, capsules, and powders.

19. (Original) The composition according to Claim 17, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 50 μm to about 150 μm.

20. (Original) The composition according to Claim 19, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 80 μm to about 130 μm.

21. (Original) The composition according to Claim 17, wherein the granules have a granule D_{50} effective to release from about 70% to about 110% of the target amount of the calcium-receptor active compound from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

22. (Original) The composition according to Claim 21, wherein the granules have a granule D_{50} effective to release at least about 75% of the target amount of the calcium-receptor active compound from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

23. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is present in a therapeutically effective amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

24. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is present in an effective dosage amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

25. (Original) The composition according to Claim 23, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

26. (Original) The composition according to Claim 24, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

27. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is present in an amount ranging from about 1% to about 70% by weight relative to the total weight of the composition.

28. (Original) The composition according to Claim 27, wherein the cinacalcet HCl is present in an amount ranging from about 5% to about 40% by weight relative to the total weight of the composition.

29. (Original) The composition according to Claim 28, wherein the cinacalcet HCl is present in an amount ranging from about 15% to about 20% by weight relative to the total weight of the composition.

30. (Original) The composition according to Claim 1, wherein the at least one pharmaceutically acceptable excipient is chosen from non-cellulose and cellulose diluents, binders, and disintegrants.

31. (Original) The composition according to Claim 1, wherein the at least one pharmaceutically acceptable excipient is chosen from microcystalline cellulose, starch, talc, povidone, crospovidone, magnesium stearate, colloidal silicon dioxide, and sodium dodecyl sulfate and any combination thereof.

32-38. (Withdrawn)

39. (Original) The composition according to Claim 31, wherein the microcystalline cellulose is present in an amount ranging from about 25% to about 85% by weight relative to the total weight of the composition.

40-42. (Withdrawn)

43. (Original) The composition according to Claim 1 comprising:

(a) from about 10% to about 40% by weight of cinacalcet HCl or cinacalcet methanesulfonate;

(b) from about 45% to about 85% by weight of at least one diluent;

(c) from about 1% to about 5% by weight of at least one binder;

(d) from about 1% to about 10% by weight of at least one disintegrant; and

(e) from about 0.05% to about 5% of at least one additive chosen from glidants, lubricants, and adherents;

wherein the percentage by weight is relative to the total weight of the composition.

44-45. (Withdrawn)

46. (Original) The composition according to Claim 43, further comprising at least one ingredient chosen from lubricants and clear and color coating materials.

47. (Original) The composition according to Claim 43 further comprising from about 1% to about 6% by weight of at least one coating material chosen from clear and color coating materials relative to the total weight of the composition.

48-51. (Withdrawn)

52. (Original) The composition according to Claim 12, wherein the effective dosage amount of cinacalcet HCl ranges from about 1 mg to about 360 mg.

53. (Original) The composition according to Claim 52, wherein the effective dosage amount of cinacalcet HCl ranges from about 5 mg to about 240 mg.

54. (Original) The composition according to Claim 52, wherein the effective dosage amount of cinacalcet HCl ranges from about 20 mg to about 100 mg.

55. (Original) The composition according to claim 52, wherein the effective dosage amount of cinacalcet HCl is chosen from about 5 mg, about 15, mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, and about 360 mg.

56. (Original) The composition according to Claim 12, wherein the therapeutically effective amount of cinacalcet HCl ranges from about 1 mg to about 360 mg.

57. (Original) The composition according to Claim 56, wherein the therapeutically effective amount of cinacalcet HCl ranges from about 5 mg to about 240 mg.

58. (Original) The composition according to Claim 56, wherein the therapeutically effective amount of cinacalcet HCl ranges from 20 mg to 100 mg.

59. (Original) The composition according to claim 56, wherein the therapeutically effective amount of cinacalcet HCl is chosen from about 5 mg, about 15, mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, and about 360 mg.

60. (Currently Amended) A pharmaceutical composition comprising an effective dosage amount of a ~~calcium receptor active~~ calcimimetic compound or a calcilytic compound and at least one pharmaceutically acceptable excipient, herein at least one dosage unit of the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37 °C ±0.5°C, and at a rotation speed of 75 r.p.m., which comprises from 50% to 125% of a target amount of the ~~calcium receptor active~~ calcimimetic compound or the calcilytic compound being released from the composition no later than 30 minutes from the start of the test.

61-77. (Withdrawn)

78. (Original) A pharmaceutical composition comprising
(a) from about 10% to about 40% by weight of cinacalcet HCl;
(b) from about 45% to about 85% by weight of at least one diluent; and
(c) from about 1% to about 5% by weight of at least one binder;
wherein the percentage by weight is relative to the total weight of the composition.

79. (Original) The composition according to Claim 78 further comprising from about 1% to about 10% by weight of at least one disintegrant, wherein the percentage by weight is relative to the total weight of the composition.

80. (Original) The composition according to Claim 78 further comprising from about 0.05% to about 5% of at least one additive chosen from glidants, lubricants, and adherents, wherein the percentage by weight is relative to the total weight of the composition.

81-82. (Withdrawn)

83. (Original) The composition according to Claim 78 further comprising at least one ingredient chosen from lubricants and clear and color coating materials.

84. (Original) The composition according to Claim 78 further comprising from about 1% to about 6% by weight of at least one coating material chosen from clear and color coating materials relative to the total weight of the composition.

85. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is in a form chosen from amorphous powders, crystalline particles, matrix particles, and mixtures of any of the foregoing.

86. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is in a form chosen from needle-shape particles, rod-shape particles, plate-shaped particles, and mixtures of any of the foregoing.

87. (Original) The composition according to Claim 78, wherein the particle D_{50} of the cinacalcet HCl particles is less than or equal to about 50 μm.

88. (Original) The composition according to Claim 78, wherein the composition is in the form of granules.

89. (Original) The composition according to Claim 78, wherein the composition is in a form chosen from tablets, capsules, and powders.

90. (Original) The composition according to Claim 88, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 50 μm to about 150 μm.

91. (Original) The composition according to Claim 90, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 80 μm to about 130 μm.

92. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is present in a therapeutically effective amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

93. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is present in an effective dosage amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

94. (Original) The composition according to Claim 92, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

95. (Original) The composition according to Claim 93, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

96. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is present in an amount ranging from about 10% to about 30% by weight relative to the total weight of the composition.

97. (Original) The composition according to Claim 96, wherein the cinacalcet HCl is present in an amount ranging from about 15% to about 20% by weight relative to the total weight of the composition.

98. (Withdrawn)

99. (Currently Amended) The composition according to claim ~~98~~ 78, wherein the microcrystalline cellulose is present in an amount ranging from about 40% to about 75% by weight, and the starch is present in an amount ranging from about 5% to about 10% by weight, relative to the total weight of the composition.

100-118. (Withdrawn)

Atty. Docket No. A-870-US-NP

Remarks

Claims 1, 3, 12, 60 and 99 have been amended. Applicants believe no new matter is present in the present amendment. Entry of the amendment is thus respectfully requested.

Claim Rejection – 35 USC §112

Claims 1-31, 39, 42, 46-47, 52-60 stand rejected under 35 U.S.C §112, first paragraph, as allegedly failing to comply with the written description requirement. While Applicants do not concede that this claim has been, or could be properly rejected for failing to comply with the written description requirement, claim 1 is amended to expedite the prosecution of the application. Support for the amendment resides, *inter alia*, on page 1, section 9, or claim 2. The amendment does not add new matter, and its entry is respectfully requested.

Claim Rejection – 35 USC §102

Claims 1-5, 7-11 and 18 stand rejected under 35 USC §102(b) as allegedly being anticipated by Nemeth et al. (USP 6,031,003, herein referred to as '003). Applicants respectfully submit that while Nemeth discloses pharmaceutical composition comprising calcium-receptor modulator agents such as calcimimetics that can be formulated as pharmaceutically acceptable salts such as hydrochloride, acetate and the like, Nemeth does not teach each and every element of the present invention. Patent '003 does not disclose pharmaceutical compositions of the same physiochemical properties, such as dissolution profile. The present invention encompasses only pharmaceutical compositions comprising a calcimimetic compound or a calcilytic compound and possessing a certain dissolution profile, which is measured under certain conditions using a defined apparatus. The dissolution profile of the compositions of the instant invention defines the rate of drug release from the inventive composition, the bioavailability of the calcimimetic or calcilytic compound, and, ultimately, its *in vivo* performance. Patent '003 does not teach pharmaceutical compositions characterized by the same dissolution profile as the pharmaceutical compositions of the present invention.

Claims 12 and 23-29 stand rejected as allegedly being anticipated by William G. Goodman et al. (J. Am. Soc. Nephrology 13, 1017-1024, 2002). Applicants respectfully submit that Goodman et al. does not teach each and every element of the present invention. Claim 12 depends from claim 1, and therefore incorporates all limitations of this claim. Goodman et al does not teach pharmaceutical compositions comprising cinacalcet HCl and possessing a certain

dissolution profile, which is measured under certain conditions using a defined apparatus. Applicants respectfully submit that this rejection should be withdrawn.

Claim Rejection – 35 USC §103

Claims 1-31, 39, 43, 46-47, 52-60, 78-80, 83-97 and 99 stand rejection under 35 USC §103(a) as allegedly being unpatentable over Goodman et al. (supra) in view of Ault et al (US 2002/0123459) or Black et al (US 2001/0051636) or Krumhar et al (USP 6,447, 809).

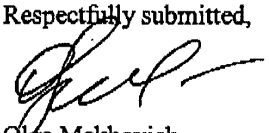
Applicants respectfully disagree. For the reasons stated above, Goodman et al. does not teach the present pharmaceutical compositions with the defined dissolution profile. Further, neither Ault, nor Black nor Krumhar et al disclose pharmaceutical compositions comprising a compound chemically and physically unrelated to a calcimimetic or a calcilytic compound of the inventive compositions. Thus, one skilled in the art would not be able to combine these references drawn to unrelated compositions which do not possess the dissolution profile of the compositions of the present invention and combine them to arrive to the claimed invention. Applicants thus respectfully request that this rejection be withdrawn.

Reconsideration and the allowance of the pending claims are thus respectfully requested. The foregoing amendments and remarks address each issue raised by the Examiner and Applicants believe they place the claims in condition for allowance. If, however, any issues remain that the undersigned can help resolve, the Examiner is invited to contact her directly at the telephone number below so that they can be promptly resolved.

Please send all future correspondence to

Customer No. 30174
Amgen Inc.
1120 Veterans Boulevard
South San Francisco, CA 94080
Phone: 650-244-2245
Fax: 650-837-9422

Respectfully submitted,



Olga Mekhovich
Limited Recognition No. L0066
Attorney for Applicants
Dated: December 21, 2007

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PTO/SB/22 (10-07)
Approved for use through 10/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE
Under the paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2008 (Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)	Docket Number (Optional) A-870-US-NP
Application Number 10/937,870	Filed September 10, 2004
For Rapid Dissolution Formulation of a Calcium Receptor-Active Compound	
Art Unit 1618	Examiner Jagadishwar R. Samala

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$120	$60	$
☑ Two months (37 CFR 1.17(a)(2))	$460	$230	$ 460.00
☐ Three months (37 CFR 1.17(a)(3))	$1050	$525	$
☐ Four months (37 CFR 1.17(a)(4))	$1640	$820	$
☐ Five months (37 CFR 1.17(a)(5))	$2230	$1115	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

12/26/2007 HLE333 00000050 010519 10937870
01 FC:1252 460.00 DA

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 01-0519. I have enclosed a duplicate copy of this sheet.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number L0066

☐ attorney or agent under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature — December 21, 2007 (Date)

Olga Mekhovich (Typed or printed name) — 650-244-2245 (Telephone Number)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/937,870	09/10/2004	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/21/2007	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 62	Minus	** 118	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***11	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
Henrietta K. Dendy

UNITED STATES PATENT AND TRADEMARK OFFICE

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30174 e 01/11/2008

AMGEN INC.
1120 VETERANS BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

Paper No.

Application No.:	**10/937,870**	**Date Mailed:**	**01/11/2008**
First Named Inventor:	Lawrence, Glen, Gary	Examiner:	SAMALA, JAGADISHWAR RAO
Attorney Docket No.:	A-870-US-NP	Art Unit:	1618
Confirmation No.:	1696	Filing Date:	09/10/2004

Please find attached an Office communication concerning this application or proceeding.

Commissioner for Patents

PTO-90c (Rev.08-06)

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No. 10/937,870	Applicant(s) LAWRENCE ET AL.	
		Art Unit 1600	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

The amendment document filed on *21 December, 2007* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☒ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☐ E. Other: _____.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4): For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance, or a drawing submission (only) If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a Quayle action. If any of above boxes 1 to 4 are checked, the correction required is only the corrected section of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.
   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

Legal Instruments Examiner (LIE), if applicable Henrietta K. Dendy Telephone No: 5712720517

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	**Glen Lawrence et al.**	Docket No.:	**A-870-US-NP**
Serial No.:	**10/937,870**	Group Art Unit No.:	**1618**
Filed:	**09/10/2004**	Examiner:	**Jagadishwar R. Samala**

For: **Rapid Dissolution Formulation of a Calcium Receptor-Active Compound**

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

In response to the Notice of Non-Compliant Amendment mailed January 11, 2008, Applicants hereby submit a complete "Listing of Claims," specifically including the text of the withdrawn claims.

Amendments to the claims are reflected in the listing of claims beginning on page 2 of this paper.

Remarks begin on page 21 of this paper.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper (along with any referred to as being attached or enclosed) (22 pages total) is being facsimile transmitted to the United States Patent and Trademark Office, 571.273.8300, on the date shown below:

February 4, 2008 — Julie M. Balot
Date

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Atny. Docket No. A-870-US-NP

IN THE CLAIMS

Claims 1-60 and 78-112 are pending. Claims 61-77 and 113-118 are withdrawn. Claims 1-31, 39, 43, 46-47, 52-60, 78-80, 83-97 and 99 are presented for examination. Claims 1-31, 39, 43, 46-47, 52-60, 78-80, 83-97 and 99 are rejected.

Please enter the following listing of claims, which will replace all prior versions, and listings, of claims in the application:

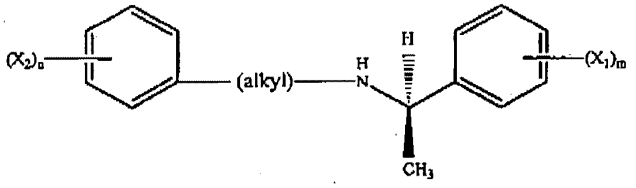
Listing of Claims

1. (Currently Amended) A pharmaceutical composition comprising an effective dosage amount of a calcimimetic compound or a calcilytic compound and at least one pharmaceutically acceptable excipient,

wherein at least one dosage unit of the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the ~~calcium receptor-active~~ calcimimetic compound or the calcilytic compound being released from the composition no later than about 30 minutes from the start of the test.

2. (Canceled).

3. (Currently Amended) The composition according to Claim 1 ~~2~~, wherein the calcimimetic compounds and calcilytic compounds are chosen from compounds of formula (I) and pharmaceutically acceptable salts and forms thereof



(I)

wherein:

PAGE 2/22 * RCVD AT 2/4/2008 8:18:07 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/7 * DNIS:2738300 * CSID:6508379422 * DURATION (mm-ss):03-28

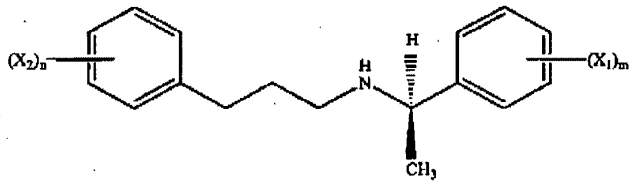
X_1 and X_2, which may be identical or different, are each a radical chosen from CH_3, CH_3O, CH_3CH_2O, Br, Cl, F, CF_3, CHF_2, CH_2F, CF_3O, CH_3S, OH, CH_2OH, $CONH_2$, CN, NO_2, CH_3CH_2, propyl, isopropyl, butyl, isobutyl, t-butyl, acetoxy, and acetyl radicals, or two of X_1 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical, or two of X_2 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical; provided that X_2 is not a 3-t-butyl radical;

n ranges from 0 to 5;

m ranges from 1 to 5; and

the alkyl radical is chosen from C1-C3 alkyl radicals, which are optionally substituted with at least one group chosen from saturated and unsaturated, linear, branched, and cyclic C1-C9 alkyl groups, dihydroindolyl and thiodihydroindolyl groups, and 2-, 3-, and 4-piperid(in)yl groups; and the stereoisomers thereof.

4. (Original) The composition according to Claim 3, wherein the calcimimetic compounds and calcilytic compounds are chosen from compounds of formula (II) and pharmaceutically acceptable salts and forms thereof



(II)

wherein:

X_1 and X_2, which may be identical or different, are each a radical chosen from CH_3, CH_3O, CH_3CH_2O, Br, Cl, F, CF_3, CHF_2, CH_2F, CF_3O, CH_3S, OH, CH_2OH, $CONH_2$, CN, NO_2, CH_3CH_2, propyl, isopropyl, butyl, isobutyl, t-butyl, acetoxy, and acetyl radicals, or two of X_1 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical, or two of X_2 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical; provided that X_2 is not a 3-t-butyl radical;

n ranges from 0 to 5; and
m ranges from 1 to 5.

5. (Original) The composition according to Claim 4, wherein the pharmaceutically acceptable salts and forms thereof are chosen from salts of hydrochloric acid and salts of methanesulfonic acid.

6. (Original) The composition according to Claim 4, wherein the calcimimetic compounds are chosen from cinacalcet, cinacalcet HCl, and cinacalcet methanesulfonate.

7. (Original) The composition according to Claim 1, wherein the dissolution profile comprises from about 70% to about 110% of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

8. (Original) The composition according to Claim 7, wherein the dissolution profile comprises at least about 75% of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

9. (Original) The composition according to Claim 6, wherein the dissolution profile comprises from about 70% to about 110% of the target amount of the cinacalcet HCl being released from the composition no later than about 30 minutes from the start of the test.

10. (Original) The composition according to Claim 9, wherein the dissolution profile comprises at least about 75% of the target amount of the cinacalcet HCl being released from the composition no later than about 30 minutes from the start of the test.

11. (Original) The composition according to Claim 6, wherein the cinacalcet HCl and cinacalcet methanesulfonate are in a form chosen from amorphous powders, crystalline particles and mixtures thereof.

12. (Currently Amended) The composition according to Claim 1, wherein the ~~calcium receptor active~~ calcimimetic compound is cinacalcet HCl.

13. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is in a form chosen from needle-shape particles, rod-shape particles, plate-shaped particles, and mixtures of any of the foregoing.

14. (Original) The composition according to Claim 12, wherein the particle D_{50} of the cinacalcet HCl particles is less than or equal to about 50 μm.

15. (Original) The composition according to Claim 12, wherein the cinacalcet HCl particles have a particle D_{50} effective to release from about 70% to about 110% of the target amount of the cinacalcet HCl from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

16. (Original) The composition according to Claim 15, wherein the cinacalcet HCl particles have a particle D_{50} effective to release at least about 75% of the target amount of the cinacalcet HCl from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

17. (Original) The composition according to Claim 1, wherein the composition is in the form of granules.

18. (Original) The composition according to Claim 1, wherein the composition is in a form chosen from tablets, capsules, and powders.

19. (Original) The composition according to Claim 17, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 50 μm to about 150 μm.

20. (Original) The composition according to Claim 19, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 80 μm to about 130 μm.

21. (Original) The composition according to Claim 17, wherein the granules have a granule D_{50} effective to release from about 70% to about 110% of the target amount of the calcium-receptor active compound from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

22. (Original) The composition according to Claim 21, wherein the granules have a granule D_{50} effective to release at least about 75% of the target amount of the calcium-receptor active compound from the composition no later than about 30 minutes from the start of the test in 0.05 N HCl.

23. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is present in a therapeutically effective amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

24. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is present in an effective dosage amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

25. (Original) The composition according to Claim 23, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

26. (Original) The composition according to Claim 24, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

27. (Original) The composition according to Claim 12, wherein the cinacalcet HCl is present in an amount ranging from about 1% to about 70% by weight relative to the total weight of the composition.

28. (Original) The composition according to Claim 27, wherein the cinacalcet HCl is present in an amount ranging from about 5% to about 40% by weight relative to the total weight of the composition.

29. (Original) The composition according to Claim 28, wherein the cinacalcet HCl is present in an amount ranging from about 15% to about 20% by weight relative to the total weight of the composition.

30. (Original) The composition according to Claim 1, wherein the at least one pharmaceutically acceptable excipient is chosen from non-cellulose and cellulose diluents, binders, and disintegrants.

31. (Original) The composition according to Claim 1, wherein the at least one pharmaceutically acceptable excipient is chosen from microcystalline cellulose, starch, talc, povidone, crospovidone, magnesium stearate, colloidal silicon dioxide, and sodium dodecyl sulfate and any combination thereof.

32. (Withdrawn) The composition according to Claim 31, wherein crospovidone is present intergranularly, intragranularly, or a combination thereof.

33. (Withdrawn) The composition according to Claim 31, wherein crospovidone is present intergranularly.

34. (Withdrawn) The composition according to Claim 31, wherein crospovidone is present intragranularly.

35. (Withdrawn) The composition according to Claim 1, wherein the composition comprises microcystalline cellulose and starch in a weight ratio ranging from about 1:1 to about 15:1.

36. (Withdrawn) The composition according to Claim 35, wherein the composition comprises microcystalline cellulose and starch in a weight ratio of about 10:1.

37. (Withdrawn) The composition according to Claim 1, wherein the granules within the composition comprises microcystalline cellulose and starch in a weight ratio ranging from about 1:1 to about 10:1.

38. (Withdrawn) The composition according to Claim 37, wherein the weight ratio between the microcystalline cellulose and the starch in the granules with the composition is about 5:1.

39. (Original) The composition according to Claim 31, wherein the microcystalline cellulose is present in an amount ranging from about 25% to about 85% by weight relative to the total weight of the composition.

40. (Withdrawn) The composition according to Claim 31, wherein the starch is present in an amount ranging from about 5% to about 35% by weight relative to the total weight of the composition.

41. (Withdrawn) The composition according to Claim 31, wherein the povidone is present in an amount ranging from about 1% to about 5% by weight relative to the total weight of the composition.

42. (Withdrawn) The composition according to Claim 31, wherein the crospovidone is present in an amount ranging from about 1% to about 10% by weight relative to the total weight of the composition.

43. (Original) The composition according to Claim 1 comprising:

(a) from about 10% to about 40% by weight of cinacalcet HCl or cinacalcet methanesulfonate;

(b) from about 45% to about 85% by weight of at least one diluent;

(c) from about 1% to about 5% by weight of at least one binder;

(d) from about 1% to about 10% by weight of at least one disintegrant; and

(e) from about 0.05% to about 5% of at least one additive chosen from glidants, lubricants, and adherents;

wherein the percentage by weight is relative to the total weight of the composition.

44. (Withdrawn) The composition according to Claim 43 comprising from about 0.05% to about 1.5% by weight of at least one glidant relative to the total weight of the composition.

45. (Withdrawn) The composition according to Claim 43 comprising from about 0.05% to about 1.5% by weight of adherent relative to the total weight of the composition.

46. (Original) The composition according to Claim 43, further comprising at least one ingredient chosen from lubricants and clear and color coating materials.

47. (Original) The composition according to Claim 43 further comprising from about 1% to about 6% by weight of at least one coating material chosen from clear and color coating materials relative to the total weight of the composition.

48. (Withdrawn) The composition according to Claim 43 comprising

(a) from about 10% to about 40% by weight of cinacalcet HCl;

(b) from about 5% to about 10% by weight of starch;

(c) from about 40% to about 75% by weight of microcrystalline cellulose;
(d) from about 1% to about 5% by weight of povidone; and
(e) from about 1% to about 10% by weight of crospovidone;
wherein the percentage by weight is relative to the total weight of the composition.

49. (Withdrawn) The composition according to Claim 48 further comprising from about 0.05% to about 1.5% by weight of colloidal silicon dioxide relative to the total weight of the composition.

50. (Withdrawn) The composition according to Claim 48 further comprising from about 0.05% to about 1.5% by weight of magnesium stearate relative to the total weight of the composition.

51. (Withdrawn) The composition according to Claim 48 further comprising from about 1% to about 6% by weight of at least one coating material chosen from clear and color coating materials relative to the total weight of the composition.

52. (Original) The composition according to Claim 12, wherein the effective dosage amount of cinacalcet HCl ranges from about 1 mg to about 360 mg.

53. (Original) The composition according to Claim 52, wherein the effective dosage amount of cinacalcet HCl ranges from about 5 mg to about 240 mg.

54. (Original) The composition according to Claim 52, wherein the effective dosage amount of cinacalcet HCl ranges from about 20 mg to about 100 mg.

55. (Original) The composition according to Claim 52, wherein the effective dosage amount of cinacalcet HCl is chosen from about 5 mg, about 15, mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, and about 360 mg.

56. (Original) The composition according to Claim 12, wherein the therapeutically effective amount of cinacalcet HCl ranges from about 1 mg to about 360 mg.

57. (Original) The composition according to Claim 56, wherein the therapeutically effective amount of cinacalcet HCl ranges from about 5 mg to about 240 mg.

58. (Original) The composition according to Claim 56, wherein the therapeutically effective amount of cinacalcet HCl ranges from 20 mg to 100 mg.

59. (Original) The composition according to Claim 56, wherein the therapeutically effective amount of cinacalcet HCl is chosen from about 5 mg, about 15, mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, and about 360 mg.

60. (Currently Amended) A pharmaceutical composition comprising an effective dosage amount of a ~~calcium receptor-active~~ calcimimetic compound or a calcilytic compound and at least one pharmaceutically acceptable excipient, herein at least one dosage unit of the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37°C ±0.5°C, and at a rotation speed of 75 r.p.m., which comprises from 50% to 125% of a target amount of the ~~calcium receptor-active~~ calcimimetic compound or the calcilytic compound being released from the composition no later than 30 minutes from the start of the test.

61. (Withdrawn) A method of making a pharmaceutical composition comprising:

(a) forming a granule comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient; and

(b) controlling the particle size of the granule such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test

conducted in a USP 2 apparatus at a temperature of about 37°C, and a rotation speed of about 75 r.p.m.

62. (Withdrawn) A method of making a pharmaceutical composition comprising:

(a) forming a granule comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient; and

(b) controlling the particle size of the granule such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37°C ±0.5°C, and a rotation speed of 75 r.p.m.

63. (Withdrawn) A method of making a pharmaceutical composition comprising:

(a) forming a composition comprising an effective dosage amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient; and

(b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37°C, and a rotation speed of about 75 r.p.m.

64. (Withdrawn) A method of making a pharmaceutical composition comprising:

(a) forming a composition comprising an effective dosage amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient; and

(b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37°C ±(0.5)°C, and a rotation speed of 75 r.p.m.

65. (Withdrawn) A method of making a pharmaceutical composition comprising forming a granule comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient in a granulator,

wherein the granulator has a volume ranging from about 1 L to about 2000 L, and

wherein the granulator contains water in a granulation level ranging from about 10% to about 50% relative to the weight of the dry powders in the granulator.

66. (Withdrawn) The method according to Claim 65, wherein the granulator has a volume ranging from about 65 L to about 1200 L.

67. (Withdrawn) The method according to Claim 65, wherein the granulator has a volume ranging from about 300 L to about 800 L.

68. (Withdrawn) The method according to Claim 65, wherein the water is in a granulation level ranging from about 20% to about 40% relative to the weight of the dry powders in the granulator.

69. (Withdrawn) The method according to Claim 65, wherein the water is in a granulation level ranging from about 30% to about 36% relative to the weight of the dry powders in the granulator.

70. (Withdrawn) The method according to Claim 65, wherein the granulator has a impeller, whose tip speed ranges from about 5 m/s to about 10 m/s.

71. (Withdrawn) The method according to Claim 70, wherein the impeller tip speed ranges from about 7 m/s to about 9 m/s.

72. (Withdrawn) A method for the treatment of at least one disease chosen from hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product, comprising administering to a patient in need thereof a pharmaceutical composition

comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient,

wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

73. (Withdrawn) The method according to Claim 72, wherein the patient is human.

74. (Withdrawn) The method according to Claim 72, wherein an effective dosage amount of the pharmaceutical composition is chosen from about 5 mg, about 15 mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, and about 360 mg.

75. (Withdrawn) A method for the treatment of at least one disease chosen from hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product, comprising administering to a patient in need thereof a pharmaceutical composition comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient,

wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37 °C ±0.5 °C, and at a rotation speed of 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

76. (Withdrawn) The method according to Claim 75, wherein the patient is human.

77. (Withdrawn) The method according to Claim 75, wherein an effective dosage amount of the pharmaceutical composition is chosen from about 5 mg, about 15 mg, about 30 mg, about

50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, and about 360 mg.

78. (Original) A pharmaceutical composition comprising
(a) from about 10% to about 40% by weight of cinacalcet HCl;
(b) from about 45% to about 85% by weight of at least one diluent; and
(c) from about 1% to about 5% by weight of at least one binder;
wherein the percentage by weight is relative to the total weight of the composition.

79. (Original) The composition according to Claim 78 further comprising from about 1% to about 10% by weight of at least one disintegrant, wherein the percentage by weight is relative to the total weight of the composition.

80. (Original) The composition according to Claim 78 further comprising from about 0.05% to about 5% of at least one additive chosen from glidants, lubricants, and adherents, wherein the percentage by weight is relative to the total weight of the composition.

81. (Withdrawn) The composition according to Claim 80 comprising from about 0.05% to about 1.5% by weight of at least one glidant.

82. (Withdrawn) The composition according to Claim 80 comprising from about 0.05% to about 1.5% by weight of adherent.

83. (Original) The composition according to Claim 78 further comprising at least one ingredient chosen from lubricants and clear and color coating materials.

84. (Original) The composition according to Claim 78 further comprising from about 1% to about 6% by weight of at least one coating material chosen from clear and color coating materials relative to the total weight of the composition.

85. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is in a form chosen from amorphous powders, crystalline particles, matrix particles, and mixtures of any of the foregoing.

86. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is in a form chosen from needle-shape particles, rod-shape particles, plate-shaped particles, and mixtures of any of the foregoing.

87. (Original) The composition according to Claim 78, wherein the particle D_{50} of the cinacalcet HCl particles is less than or equal to about 50 μm.

88. (Original) The composition according to Claim 78, wherein the composition is in the form of granules.

89. (Original) The composition according to Claim 78, wherein the composition is in a form chosen from tablets, capsules, and powders.

90. (Original) The composition according to Claim 88, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 50 μm to about 150 μm.

91. (Original) The composition according to Claim 90, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 80 μm to about 130 μm.

92. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is present in a therapeutically effective amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

93. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is present in an effective dosage amount for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

94. (Original) The composition according to Claim 92, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

95. (Original) The composition according to Claim 93, wherein the hyperparathyroidism is chosen from primary hyperparathyroidism and secondary hyperparathyroidism.

96. (Original) The composition according to Claim 78, wherein the cinacalcet HCl is present in an amount ranging from about 10% to about 30% by weight relative to the total weight of the composition.

97. (Original) The composition according to Claim 96, wherein the cinacalcet HCl is present in an amount ranging from about 15% to about 20% by weight relative to the total weight of the composition.

98. (Withdrawn) The composition according to Claim 78, wherein the at least one diluent is chosen from microcystalline cellulose, starch, and mixtures thereof.

99. (Currently Amended) The composition according to Claim ~~98~~ 78, wherein the microcrystalline cellulose is present in an amount ranging from about 40% to about 75% by weight, and the starch is present in an amount ranging from about 5% to about 10% by weight, relative to the total weight of the composition.

100. (Withdrawn) The composition according to Claim 78, wherein the at least one binder is povidone.

101. (Withdrawn) The composition according to Claim 100, wherein the povidone is present in an amount ranging from about 1% to about 5% by weight, relative to the total weight of the composition.

102. (Withdrawn) The composition according to Claim 78, wherein the at least one disintegrant is crospovidone.

103. (Withdrawn) The composition according to Claim 102, wherein crospovidone is present intergranularly, intragranularly, or a combination thereof.

104. (Withdrawn) The composition according to Claim 102, wherein crospovidone is present intergranularly.

105. (Withdrawn) The composition according to Claim 102, wherein crospovidone is present intragranularly.

106. (Withdrawn) The composition according to Claim 98, wherein the composition comprises microcystalline cellulose and starch in a weight ratio ranging from about 1:1 to about 15:1.

107. (Withdrawn) The composition according to Claim 106, wherein the composition comprises microcystalline cellulose and starch in a weight ratio of about 10:1.

108. (Withdrawn) The composition according to Claim 98, wherein the granules within the composition comprises microcystalline cellulose and starch in a weight ratio ranging from about 1:1 to about 10:1.

109. (Withdrawn) The composition according to Claim 108, wherein the weight ratio between the microcystalline cellulose and the starch in the granules with the composition is about 5:1.

110. (Withdrawn) The composition according to Claim 78 comprising

(a) from about 10% to about 40% by weight of cinacalcet HCl;

(b) from about 5% to about 10% by weight of starch;

(c) from about 40% to about 75% by weight of microcrystalline cellulose;

(d) from about 1% to about 5% by weight of povidone; and

(e) from about 1% to about 10% by weight of crospovidone;

wherein the percentage by weight is relative to the total weight of the composition.

111. (Withdrawn) The composition according to Claim 110 further comprising from about 0.05% to about 1.5% by weight of colloidal silicon dioxide relative to the total weight of the composition.

112. (Withdrawn) The composition according to Claim 110 further comprising from about 0.05% to about 1.5% by weight of magnesium stearate relative to the total weight of the composition.

113. (Withdrawn) A method of controlling the dissolution rate of a formulation comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient, the method comprising producing the formulation in a granulator which has a volume ranging from about 1 L to about 2000 L, and contains water in a granulation level ranging from about 10% to 50% relative to the amount of dry powders in the granulator.

114. (Withdrawn) The method according to Claim 113, wherein the calcium receptor-active compound is cinacalcet HCl.

115. (Withdrawn) The method according to Claim 113, wherein the granulator has a volume ranging from about 65 L to about 1200 L.

116. (Withdrawn) The method according to Claim 113, wherein the granulator has a volume ranging from about 300 L to about 800 L.

117. (Withdrawn) The method according to Claim 113, wherein the water is in a granulation level ranging from about 20% to about 40% relative to the weight of the dry powders in the granulator.

118. (Withdrawn) The method according to Claim 117, wherein the water is in a granulation level ranging from about 30% to about 36% relative to the weight of the dry powders in the granulator.

Atny. Docket No. A-870-US-NP

Remarks

Applicants believe that the requirements of 37 CFR 1.121 or 1.4 have been met by providing a listing of all pending claims (specifically including the withdrawn claims) contained herein. Reconsideration and the allowance of the pending claims are thus respectfully requested.

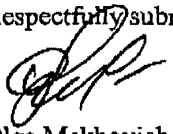
Applicants believe that no fee is due in connection with this Response. However, should any additional fees be required, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 01-0519. A copy of this sheet is enclosed for such purpose.

If any issues remain that the undersigned can help resolve, the Examiner is invited to contact her directly at the telephone number below so that they can be promptly resolved.

Please send all future correspondence to

Customer No. 30174
Amgen Inc.
1120 Veterans Boulevard
South San Francisco, CA 94080
Phone: 650-244-2245
Fax: 650-837-9422

Respectfully submitted,



Olga Mekhovich
Limited Recognition No. L0066
Attorney for Applicants
Dated: February 4, 2008.

Atny. Docket No. A-870-US-NP

COPY

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Respectfully submitted,

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Attorney for Applicants
Dated: February 4, 2008.

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/937,870	09/10/2004	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	02/04/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 117	Minus	** 118	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 11	Minus	***11	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/LINDA W. BADIE/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/937,870	09/10/2004	Glen Gary Lawrence	A-870-US-NP	1696

30174 7590 04/14/2008

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SAMALA, JAGADISHWAR RAO	
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The time period for reply, if any, is set in the attached communication.