(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 184 377 A1

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
06.03.2002 Bulletin 2002/10

(51) Int Cl.[7]: **C07D 257/10**, A61K 49/00

(21) Application number: **01127327.3**

(22) Date of filing: **29.09.1994**

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **30.09.1993 US 129870**

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
94926365.1 / 0 670 832

(71) Applicant: **BRACCO International B.V.**
1083 HJ Amsterdam (NL)

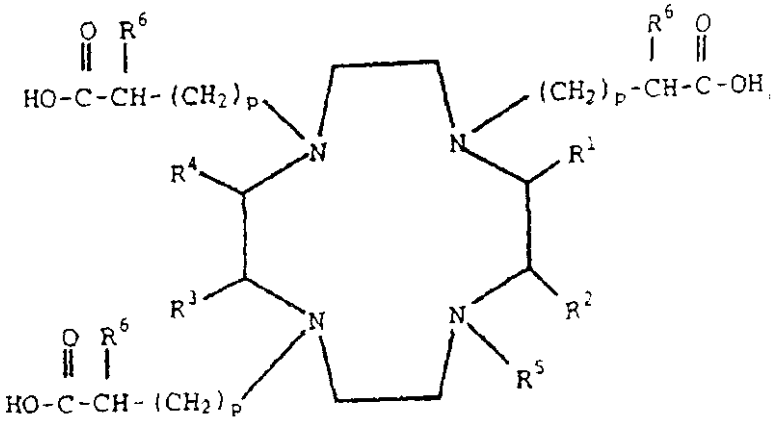
(72) Inventors:
- **Desreux, Jean-Francois**
  400 Anglecur (BE)
- **Tweedle, Michael F.**
  Princeton, NJ 08540 (US)
- **Ratsep, Peter C.**
  Hamilton Square, NJ 08690 (US)
- **Wagler, Thomas R.**
  Princeton, NJ 08540 (US)
- **Marinelli, Edmund R.**
  Lawrenceville, NJ 03646 (US)

(74) Representative: **De Carli, Elda**
c/o Bracco Imaging SpA, Via E. Folli, 50
20134 Milano (IT)

Remarks:
This application was filed on 20 - 11 - 2001 as a divisional application to the application mentioned under INID code 62.

(54) **Hepatobiliary magnetic resonance contrast agents**

(57) A compound of the formula:



wherein

R^1 and R^2 are both hydrogen and R^3 and R^4 together with the carbon atoms in the tetraazacyclododecane macrocycle to which they are attached form a fused fully or partially saturated non aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, straight or branched (C_1-C_5)alkyl, alkyl oxide of formula -R-OR wherein each R is a straight or branched (C_1-C_5)alkyl, hydroxy or hydroxyalkyl groups, and which may be further fused to a phenyl or cyclohexyl ring

EP 1 184 377 A1

R^5 is $-(CH_2)_p-CH(R^6)-C(=O)-OH$

p is 0 or 1 and R_6 is hydrogen or a straight or branched (C_1-C_5) alkyl group; or a salt thereof and the metal chelates thereof, particularly gadolinium chelates, the pharmaceutical and diagnostic compositions containing them and their use in MRI.

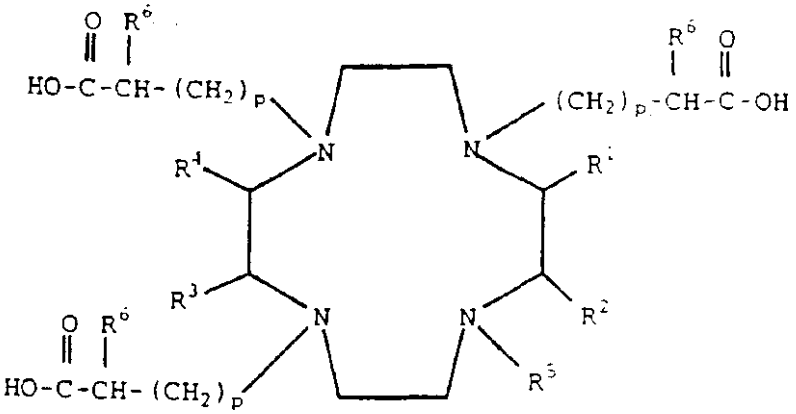
Description

Brief Description of the Invention

[0001] In accordance with the present invention, novel compounds are provided. These compounds are useful, for example, as metal-chelating ligands and, in the form of metal complexes, the present compounds are especially useful as diagnostic contrast agents. When the metal in the complex is paramagnetic, the diagnostic contrast agents are suitable for magnetic resonance imaging, and are particularly useful for magnetic resonance imaging (MRI)of the liver and bile ducts.

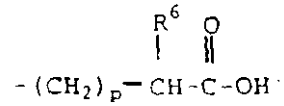
[0002] The compounds of the invention comprise a tetraazacyclododecane macrocycle containing at least one fused cyclohexyl ring, and are represented by the formula I:

I

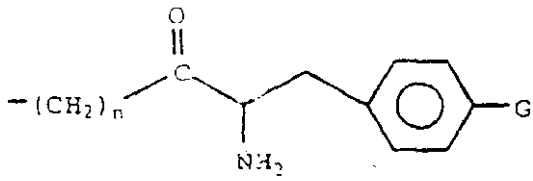


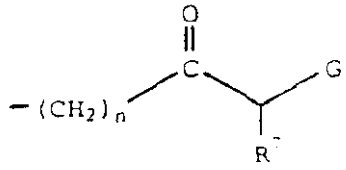
wherein

R^1 and R^2 and R^3 and R^4 independently form, together with the carbon atoms in the tetraazacyclododecane macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubsciituted or substituted by one or more halogen, alkyl, ether, hydroxy or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R^1 and R^2 are each hydrogen and R^3 and R^4 form a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R^1 and R^2 form a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above and R^3 and R^4 are hydrogen;
R^5 is

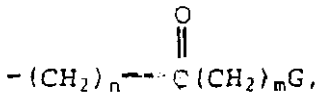


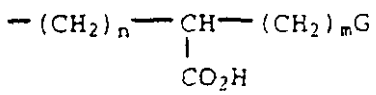
or hydrogen, alkyl, aralkyl, aryl, alkoxy, hydroxyalkyl,

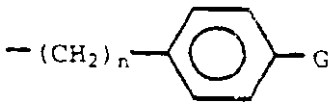




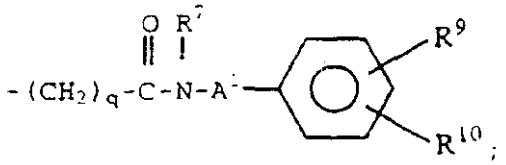
$-(CH_2)_nG$,



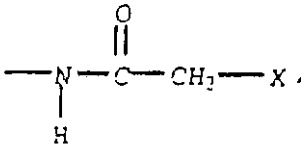




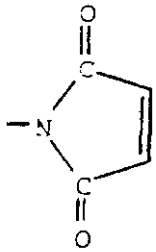
or



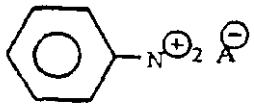
A^1 is $-(CH_2)_q-$, $-(CH{=}CH)-$, $-(CH{=}CH)_2-$ or a single bond; each $-(CH_2)_q-$ may be independently substituted with alkyl or hydroxyalkyl;
R^6 is hydrogen or alkyl;
R^7 is hydrogen, hydroxyalkyl, alkoxy, alkyl, aryl or aralkyl;
G is $-NH_2$, -NCS,



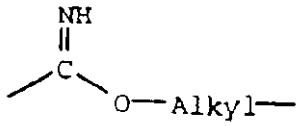
$-CO_2H$, $-NHR^8$, $-N(R^8)_2$ or -CN;



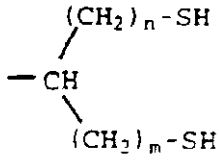
R^8 is alkyl, hydroxyalkyl,



(where A is an anion),



or



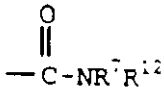
;

R^9 and R^{10} are each independently hydrogen, alkyl, $-NO_2$, $-NH_2$,



,

-NCS,



or $-NR^7COR^6$;
R^{11} is hydrogen, alkyl or hydroxyalkyl;
R^{12} is hydrogen, hydroxyalkyl, alkoxy, alkyl, aryl or aralkyl;
X is chloro, bromo or iodo;
m and n are each independently zero or an integer from one to five;
p is zero or one; and
q is an integer from 1 to 5;

and salts thereof.

Detailed Description of the Invention

[0003] Listed below are definitions of various terms used in the description of this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

[0004] The terms "alkyl" and "alkoxy" refer to both straight and branched, unsubstituted chains of carbon atoms. Those chains having 1 to 5 carbon atoms are preferred. Methyl and methoxy are the most preferred alkyl and alkoxy groups, respectively.

[0005] The term "aryl" refers to phenyl and substituted phenyl. Preferred substituted phenyl groups are those substituted with 1, 2 or 3 halogen, hydroxyl, hydroxyalkyl, alkyl, alkoxy, carbamoyl, carboxamide, acylamino or carboxyl moieties.

[0006] "Hydroxyalkyl" refers to straight and branched alkyl groups including one or more hydroxy radicals such as $-CH_2CH_2OH$, $-CH_2CH_2OHCH_2OH$, $CH(CH_2OH)_2$ and the like. (See, for example, Sovak, M., Editor, Radiocontrast Agents, Springer-Verlag, 1984, pp. 1-125).

[0007] The term "aralkyl" refers to an aryl group bonded through an alkyl group.

[0008] The term "ether" refers to an alkyl or aryl oxide of the general type -R-O-R where each R is independently alkyl or aryl.

[0009] The term "carbocyclic ring" refers to a ring system in which all the ring atoms are carbon, e.g., phenyl or cyclohexyl. The ring may be unsubstituted or substituted by, for example, alkyl, halogen, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthiol, nitro, cyano, carboxy, carbamoyl, alkoxycarbonyl, alkylsulfonyl, sulfonamido and the like.

[0010] The term "halogen" refers to bromo, chloro, fluoro or iodo.

[0011] The term "alkanoyl" refers to the group alkyl-C(O)-.

[0012] The term "alkanoyloxy" refers to the group alkyl-C(O)-O-.

[0013] The term "amino" refers to the group $-NH_2$.

[0014] The term "alkylamino" refers to the group -NHR where R is alkyl.

[0015] The term "dialkylamino" refers to the group -NRR' where R and R' are each, independently, alkyl.

[0016] The term "alkanoylamino" refers to the group alkyl-C(O)-NH-.

[0017] The term "chiol" refers to the group -SH.

[0018] The term "alkylthiol" refers to the group -SR where R is alkyl.

[0019] The term "nicro" refers to the group $-NO_2$.

[0020] The term "cyano" refers to the group -CN.

[0021] The term "carboxy" refers to the group -C(O)OH or the group -C(O)OR where R is alkyl.

[0022] The term "alkoxycarbonyl" refers to the group alkoxy-C-(O)-.

[0023] The term "alkylsulfonyl" refers to the group alkyl-SO_2-.

[0024] The term "sulfonamido" refers to the group $-SO_2NH_2$, the group $-SO_2NHR$ or the group $-SO_2NRR'$ where R and R' are each, independently, alkyl.

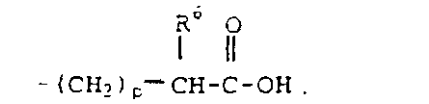
[0025] The term "carbamoyl" refers to the group $-C(O)NH_2$, the group -C(O)NHR or the group -C(O)NRR ' where R and R' are each, independently, alkyl, alkoxy or hydroxyalkyl.

[0026] The term "carboxamide" refers to the group $-C(O)NH_2$, the group -C(O)NHR or the group -C(O)NRR' where R and R' are each, independently, alkyl.

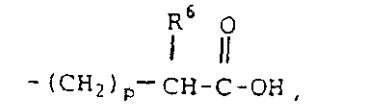
[0027] The term "acylamino" refers to the group -NH-C(O)-R where R is alkyl.

[0028] Preferred compounds of the present invention are those wherein

R^5 is



Most preferred are those compounds wherein both R^1 and R^2 and R^3 and R^4 form a fused fully saturated cyclohexyl ring, R^5 is



R^6 is -H and p is zero.

[0029] The compounds of formula I, and salts thereof, may be complexed with a paramagnetic metal atom and used as relaxation enhancement agents for magnetic resonance imaging. These agents, when administered to a mammalian

host (e.g., a human) distribute in various concentrations to different tissues, and catalyze relaxation of protons (in the tissues) that have been excited by the absorption of radiofrequency energy from a magnetic resonance imager. This acceleration of the rate of relaxation of the excited protons provides for an image of different contrast when the host is scanned with a magnetic resonance imager. The magnetic resonance imager is used to record images at various times, generally either before and after administration of the agents, or after administration only, and the differences in the images created by the agents' presence in tissues are used in diagnosis. In proton magnetic resonance imaging, paramagnetic metal atoms such as gadolinium (III), and manganese(II), chromium(III) and iron(III) (all are paramagnetic metal atoms with favorable electronic properties) are preferred as metals complexed by the ligands of formula I. Gadolinium(III) is the most preferred complexed metal due to the fact that it has the highest paramagnetism, it has low toxicity when complexed to a suitable ligand, and it has high lability of coordinated water.

[0030] The mecal-chelacing ligands of the present invention can be complexed with a lanthanide (atomic number 58 to 71) and used as chemical shift agents in magnetic resonance imaging or in magnetic resonance in vivo spectroscopy.

[0031] Paramagnetic metal complexes of the present invention are particularly useful as hepatobiliary agents, i.e., for magnetic resonance imaging of the liver and bile ducts.

[0032] While the above-described uses for the metal-chelating ligands of the present invention are preferred, those working in the diagnostic arts will appreciate that the ligands can also be complexed with the appropriate metals and used as contrast agents in other imaging techniques such as x-ray imaging, radionuclide imaging and ultrasound imaging, and in radiotherapy.

Use in Imaging

[0033] To use the ligands of the present invention for imaging, they are first complexed with an appropriate metal. This may be accomplished by methodology known in the art. For example, the metal can be added to water in the form of an oxide or in the form of a halide or acetate and treated with an equimolar amount of a ligand of the present invention. The ligand can be added as an aqueous solution or suspension. Dilute acid or base can be added (where appropriate) to maintain a suitable pH. Heating at temperatures as high as 100°C for periods of up to 24 hours or more may sometimes be employed to facilitate complexation, depending on the metal and the chelator, and their concentrations.

[0034] Pharmaceutically acceptable salts of the metal complexes of the ligands of this invention are also useful as imaging agents. They can be prepared by using a base (e.g., an alkali metal hydroxide, meglumine, arginine or lysine) to neutralize the above-prepared metal complexes while they are still in solution. Some of the metal complexes are formally uncharged and do not need cations as counterions. Such neutral complexes may be preferred as intravenously administered x-ray and NMR imaging agents over charged complexes because they may provide solutions of greater physiologic tolerance due to their lower osmolality. However, for use as hepacobiliary agents, negatively charged ligands are preferred.

[0035] The present invention provides pharmaceutical compositions comprising a compound of formula I, or a salt thereof, optionally complexed with a metal, and a pharmaceutically acceptable vehicle or diluent. The present invention further provides a method for diagnostic imaging comprising the steps of administering to a host a compound of the formula I, or a salt thereof, which is complexed with a metal, and obtaining a diagnostic image, preferably a magnetic resonance image, of said host.

[0036] Sterile aqueous solutions of the chelate complexes of the present invention are preferably administered to mammals (e.g., humans) orally, intrathecally and, especially, intravenously in concentrations of 0.003 to 1.0 molar. Use of the metal complexes of the present invention as hepatobiliary agents is preferred. For example, for visualization of the liver, the dose is preferably 0.03 to 0.3 millimole/kilogram. While visualization of the liver and bile ducts is preferred, the metal complexes of the present invention may be employed for visualization of other sites. For example, for the visualization of brain lesions using magnetic resonance imaging, a gadolinium complex of a ligand of formula I may be administered intravenously at a dose of 0.05 to 0.5 millimoles of the complex per kilogram of body weight, preferably at a dose of 0.1 to 0.3 millimoles/kilogram. For visualization of the kidneys, the dose is preferably 0.05 to 0.20 millimoles/kilogram. For visualization of the heart, the dose is preferably 0.05 to 0.3 millimoles/ kilogram.

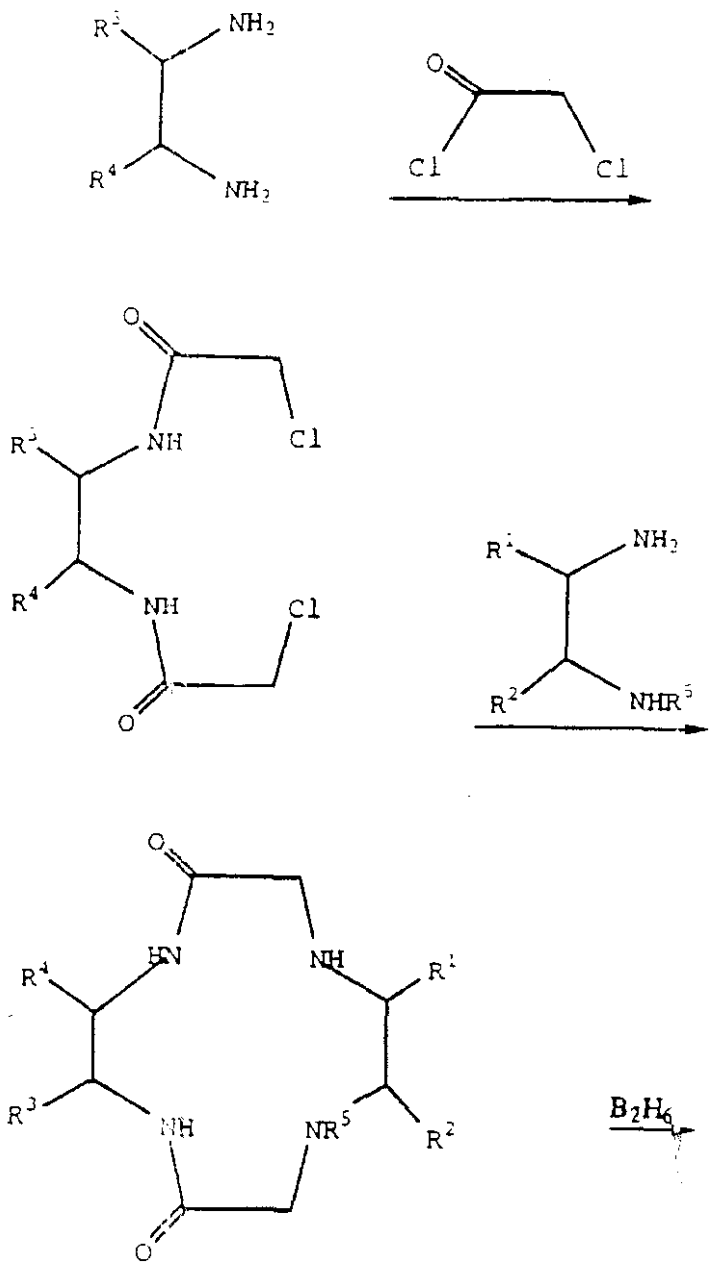
[0037] The pH of the formulation of the present metal complexes is preferably between about 6.0 and 8.0, most preferably between about 6.5 and 7.5. Physiologically acceptable buffers (e.g., tris(hydroxymethyl)-aminomethane) and other physiologically acceptable additives (e.g., stabilizers such as parabens) may also be present.

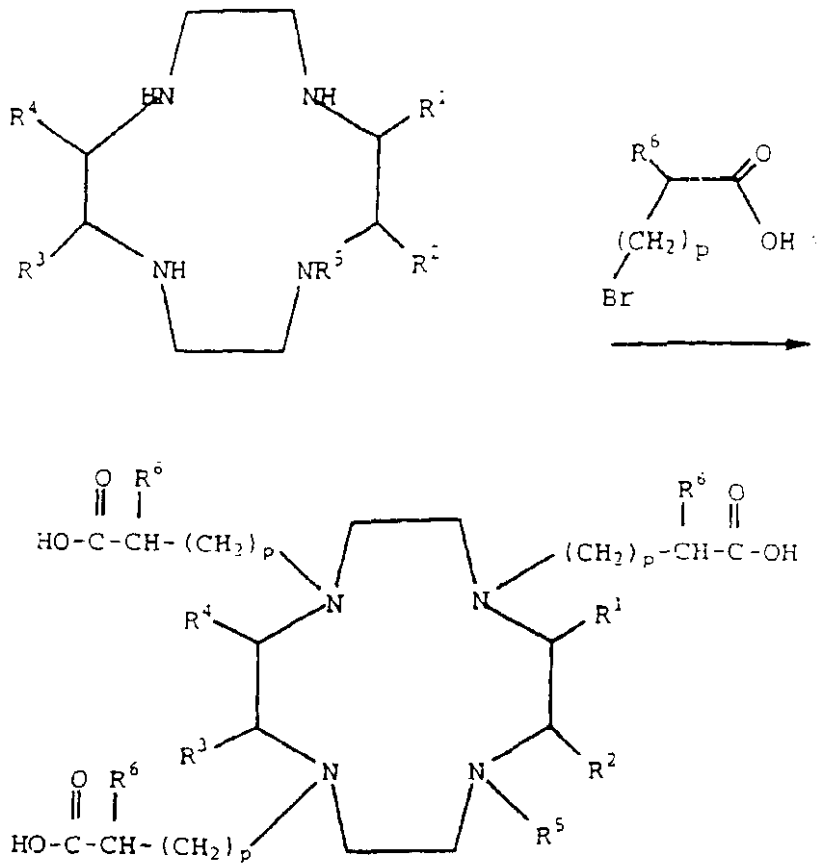
[0038] It is also advantageous to employ dual scavenging excipients such as those described in copending application U.S. Serial No. 032,763, filed March 15, 1993, entitled "DUAL FUNCTIONING EXCIPIENT FOR METAL CHELATE CONTRAST AGENTS", incorporated herein by reference. Those excipients have a general formula corresponding to:

$$D_S[D'(L')]_t$$

wherein D and D' are independently Ca or Zn, L' is an organic ligand which may be different from, or the same as, the ligand employed to complex the metal, and s and t are independently 1, 2 or 3.

[0039] The compounds of formula I can be prepared according to the following general scheme:



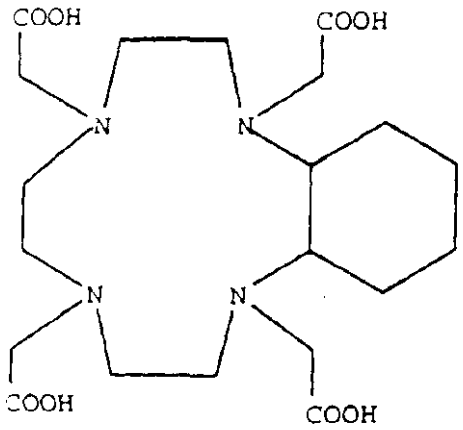


[0040] All stereoisomers of the compounds and complexes of the present invention are contemplated herein, whether alone (that is, substantially free of other isomers), in a mixture of certain stereoisomers (for example, as a racemate) or in any other mixture thereof.

[0041] The invention will now be further described by the following examples. These examples are illustrative rather than limiting.

Example 1

[0042]



2,5,8,11-Tetracarboxymethyl-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane

(A) 4,9-dioxo-2,5,8,11-tetraaza-bicyclo[10,4,0]-hexadecane

[0043] Sodium carbonate (226 g., 2.13 mol.) and trans-1,2-diaminocyclohexane (14.1 ml., 117 mmol.) were added to a solution of N,N'-dichloroacetylethylenediamine (25 g., 117 mmol.) in dry acetonitrile (3.75 l.) under nitrogen. N,N'-dichloroacetylethylenediamine was prepared as reported in "New multidentate potential ionophors of ether-amide type", Monat. Chem., 1985, 116, 217-221. The reaction mixture was refluxed for 20 hours. The insoluble material formed was filtered off and the volume of the filtrate was reduced to 1 l. by evaporation. Crystals of the monomer slowly formed at room temperature. They were collected by filtration and the product was purified by crystallization in acetonitrile. The yield was 7.43 g. of a white solid.

[0044] The acetonitrile solution obtained after filtration of compound (A) was concentrated and several fractions of crystallization were collected. The mass spectrum (FAB) and the ^1H and ^{13}C NMR spectra of each fraction was recorded and the fractions containing primarily the same compound were combined. Each fraction was crystallized twice from acetonitrile.

(B) 2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane

[0045] Dried compound (A) (2.54 g., 10 mmol.) was added under nitrogen to a 1 M solution of BH_3 in tetrahydrofuran (100 ml., 100 mmol.). The reaction mixture was refluxed overnight. After cooling, water was added dropwise until the excess of BH_3 was completely eliminated. The resulting suspension was brought to dryness in a rotary evaporator and the remaining solid was added to 140 ml. of a 6 M hydrochloric acid solution. The temperature was maintained at 100° C. overnight. Water was eliminated under vacuum and the solid residue was dissolved in a minimum amount of water. $LiOH \cdot H_2O$ was added to give a pH adjusted to 12 - 13. The mixture was extracted three times with methylene chloride. The combined organic fractions were dried (magnesium sulfate), filtered, and evaporated to give 2 g. of compound (B) as a white solid.

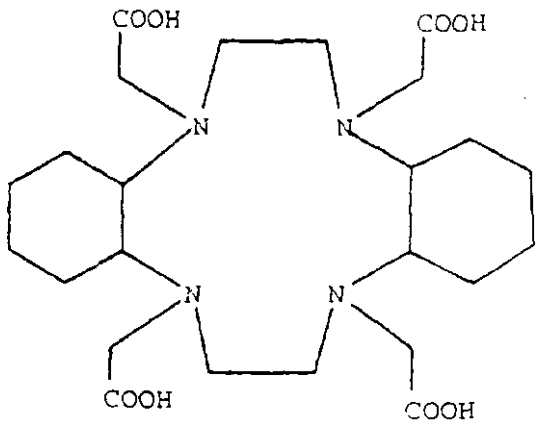
(C) 2,5,8,11-tetracarboxymethyl-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane

[0046] Bromoacetic acid (11.9 g., 86 mmol.) was dissolved in water (25 ml.). The temperature of the solution was lowered to 5° C. in an ice bath and the acid was neutralized with an aqueous solution of sodium hydroxide (3.43 g., 86 mmol. in 13 ml. water). Compound (B) (3.24 g., 14.3 mmol.) was added to the solution of sodium bromoacetate and the temperature was raised to 70 - 30° C. The pH was maintained between 9 and 10 by the dropwise addition of a solution of sodium hydroxide (3.43 g., 86 mmol.) in water (13 ml.). At the end of the addition, the temperature was maintained at 70 - 80° C. for 6 hours. The volume of the reaction mixture was then brought down to 40 ml. and the pH was acidified to 3 with 6 M hydrochloric acid. An insoluble material formed rapidly. It was filtered and recrystallized in

water until no trace of glycolic acid could be found by NMR. A second fraction of the title compound was obtained after further concentration of the reaction mixture. The two fractions were combined and 3.6 g. of the title compound as a white solid was obtained after recrystallization in water. Mass spectrum (FAB): m/e 459 (M+H) and 481 (M+Na).

Example 2

[0047]



2,5,12,15-Tetracarboxymethyl-2,5,12,15-tetraazatricyclo[14,4,0,$0^{6,11}$]icosane

(A) 3,14-dioxo-2,5,12,15-tetraazatricyclo-[14,4,0,$0^{6,11}$]icosane

[0048] N,N'-bis(chloroacetyl)-trans-1,2-diaminocyclohexane was prepared according to the procedure outlined by Saburi, M. and Yoshikawa, S., "Stereochemical studies of N-methyl-(S)-alaninato-cobalt(III) complexes with chiral tetraamines. II. Cobalt(III)-N-methyl(s)- and (R)-alaninate-N,N'-bis (β-aminoethyl)-1(R), 2(R)-diaminocyclohexane systems," Bull, Chem, Soc, Jpn., 1974, 47, 1184-1189. Anhydrous sodium carbonate (250 g., 2.36 mol.) was added to a solution of 33.4 g. (125 mmol.) of N,N'-bis(chloroacetyl)-trans-1,2-diaminocyclohexane and 15 ml. (125 mmol.) of trans-1,2-diaminocyclohexane in 3750 ml. of acetonitrile. The temperature was raised to 82° C., and the reaction mixture was violently agitated for 20 hours. At the end of the reaction, sodium carbonate was eliminated by filtration and the solvent was evaporated under vacuum. The solid residue was recrystallized from ethanol. Up to five successive batches of the desired compound were obtained after the progressive concentration of the ethanolic solution under vacuum. The yield was 9.6 g. of compound (A) as a white powder.

(B) 2,5,12,15-tetraazatricyclo[14.4.0.$0^{6,11}$]-icosane

[0049] A 1 M solution of BH_3 in tetrahydrofuran (265 ml.) was slowly added to 10.2 g. (33.1 mmol.) of compound (A). The solution was boiled for 24 hours. Water was then added dropwise to destroy the excess BH_3 and the reaction mixture was brought to dryness. The solid residue was added to 265 ml. of a 6 M hydrochloric acid solution and the mixture was refluxed overnight. Hydrochloric acid was eliminated under vacuum. The residue was digested in ethanol, filtered and dissolved in water. Concentrated ammonia was added until the pH became strongly basic. The inorganic precipitate that formed was filtered off and the filtrate was extracted with methylene chloride yielding 6.3 g. of compound (B) as a white solid after elimination of the solvent.

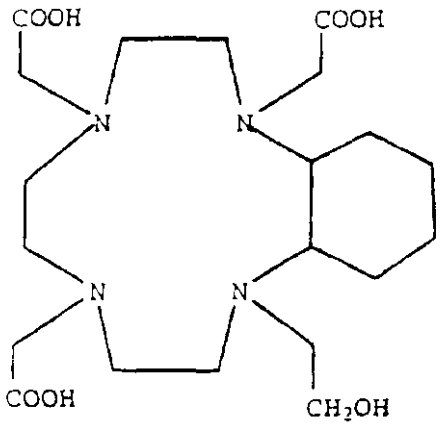
(C) 2,5,12,15-tetracarboxymethyl-2,5,12,15-tetraazatricyclo[14.4.0.$0^{6,11}$]icosane

[0050] A suspension in 90 ml. of dried dimethylformamide was prepared by mixing 1.88 g. (6.7 mmol.) of compound (B), 3.72 ml. (33.5 mmol.) of $Br\text{-}CH_2COOC_2H_5$, and 4.63 g. (33.5 mmol.) of potassium carbonate. The mixture was heated at 90° C. under nitrogen for 12 hours. The suspension was filtered and a solution of $LiOH\cdot H_2O$ (3.09 g., 73.6 mmol.) in 90 ml. water was added to the filtrate. The mixture was refluxed for 2 hours. The solvent was eliminated under vacuum and the residue was dissolved in a minimum amount of water. The pH was adjusted to 3 - 4 with con-

centrated hydrochloric acid and a colorless compound crystallized out. It was easily recrystallized in boiling water. After drying under vacuum, 1.05 g. of the title compound as a white powder was obtained. ^{13}C NMR (D_2O, 320K, strongly acid pH, ppm vs TMS): 174.2, 66.8, 66.6, 58.3, 52.8, 52.1, 49.6, 27.8, 26.9, 26.5. Mass spectrum (FAB): m/e 281 (M+H).

Example 3

[0051]



2,5,11-Tricarboxymethyl-8-(2'-hydroxyethyl)-2,5,8,11-tetraazabicyclo[10,4,0]hexadecane

(A) 3,10-dioxo-8-(2'-hydroxyethyl)-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane

[0052] Into a 5 l. erlenmeyer flask containing 5 l. of anhydrous acetonitrile was placed 17.4 g. (65 mmol.) of N,N'-bis(chloroacetyl)-trans-1,2-diaminocyclohexane (see Example 2), 6.8 g. (65 mmol.) of 2-(2-aminoethylamino)ethanol and 130 g. (1.23 mmol.) of sodium carbonate. The reaction mixture was heated at 82° C. under nitrogen for 50 hours. After eliminating sodium carbonate by filtration, acetonitrile was eliminated under vacuum until the volume was reduced to 500 ml. A precipitate formed immediately and the reaction mixture was stirred for several hours at room temperature. The precipitate was filtered off and was washed with a few ml. of acetonitrile and dried under vacuum. 8.2 g. of compound (A) was obtained as a white solid.

(B) 8-(2'-hydroxyethyl)-2,5,8,11-tetraazabicyclo[10,4,0]hexadecane

[0053] Into a dry flask under nitrogen was placed 3.00 g. (10 mmol.) of compound (A) and 100 ml. of a 1 M solution of BH_3·THF in anhydrous tetrahydrofuran. The reaction mixture was refluxed for 12 hours. Water was added dropwise until no reaction was taking place with the excess of BH_3·THF. The solvent was stripped off on a rotary evaporator after addition of a few ml. of methanol to avoid excessive foaming. The solid residue was treated with about 10 ml. of a concentrated solution of LiOF·H_2O until the pH reached 12 - 13. This aqueous phase was extracted 6 times with 100 ml. of methylene chloride. The extracts were collected and dried over magnesium sulfate. The solvent was removed under vacuum to yield 2.62 g. of Compound (B) as a white powder that was used in the next step without further purification.

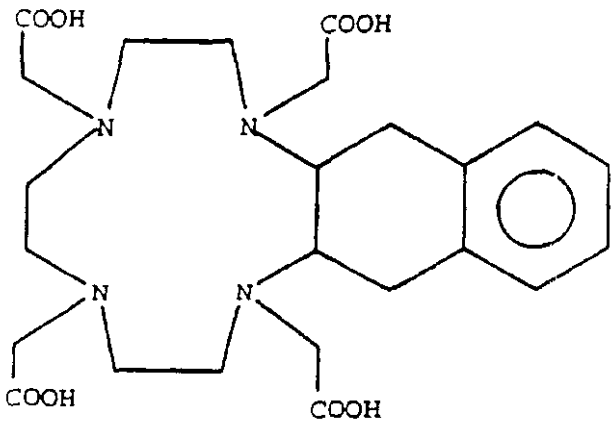
(C) 2,5,11-tricarboxymethyl-8-(2'-hydroxyethyl)-2,5,8,11-tetraazabicyclo[10,4,0]hexadecane

[0054] To a solution of 3.19 g. (23 mmol.) of bromoacetic acid in 10 ml. of water chilled in an ice bath was added dropwise 0.92 g. (23 mmol.) of sodium hydroxide dissolved in 5 ml. of water while maintaining the temperature below 5° C. This mixture was added to a solution of 1.38 g. (5.1 mmol.) of compound (B) dissolved in 5 ml. of water. The reaction mixture was heated to 70 - 80° C. and a solution of 0.92 g. of sodium hydroxide (23 mmol.) in 5 ml. of water was added dropwise while maintaining the pH in the 9 - 10 range. After completing the addition of sodium hydroxide, the reaction mixture was agitated 12 additional hours at 70 - 80°C. The reaction mixture was allowed to cool to room temperature and the pH was brought to 3 by addition of a 6 M hydrochloric acid solution. The solution was applied to

a cation exchange resin (H^+ form). After washing with water, the macrocyclic ligand was eluted with 0.5 M aqueous ammonia. Obtained after rotary evaporation was 1.66 g. of the title compound as the ammonium salt. The acid form was obtained by elution on an anion exchange column (formate form) with 0.5 M formic acid. ^{13}C NMR (D_2O, strongly acid pH, ppm vs TMS): 177.6, 175.4, 170.4, 67.7, 59.9, 57.9, 57.2, 54.9, 53.4, 52.2, 51.9, 49.9, 48.9, 48.3, 26.0 - 25.6. Mass spectrum (FAB): title compound in the acid form, m/e 445 (M+H).

Example 4

[0055]



2,5,8,11-Tetracarboxymethyl-14,15-benzo-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane

(A) 4,9-dioxo-14,15-benzo-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane

[0056] Trans-2,3-diamino-1,2,3,4-tetra-hydronaphthalene was prepared as reported by Yano, T., Kobayashi, H. and Ueno, K., "Stereospecific syntheses and acid dissociation of 2,3-diaminotetralins and 2,3-diamino-trans-decalins", Bull, Chem, Soc, Jpn., 1973 46, 985 - 990. In a 2 l. flask equipped with a mechanical stirrer and a refluxed condenser were placed 5.38 g. (33.16 mmol.) of trans-2,3-diamino-1,2,3,4-tetrahydronaphthalene and 1 l. of anhydrous acetonitrile. N, N'-dichloroacetylethylenediamine (7.06 g., 33.16 mmol.) and 64 g. (0.60 mol.) of anhydrous sodium carbonate were added to the solution. After 20 hours at 90° C., the reaction mixture was filtered and the filtrate was evaporated until the volume was reduced to 500 ml. A precipitate formed slowly when the solution was allowed to stand at room temperature overnight. It was filtered off and dried under vacuum. The yield was 5.52 g. of a brownish powder. Compound (A) was isolated by adding the powder to 500 ml. of water at 50° C. A brown viscous oil did not dissolve and was eliminated by filtration. The remaining aqueous solution was concentrated under vacuum until white crystals were formed. After letting the solution stand overnight at room temperature, 3.73 g. of compound (A) were collected by filtration. The reaction mixture left after isolation of compound (A) was concentrated further by evaporation of the acetonitrile but it yielded only the dimeric form, m.p. 230 - 231° C.

(B) 14,15-benzo-2,5,8,11-tetraaza-bicyclo-[10,4,0]hexadecane

[0057] The reduction of compound (A) was accomplished by adding 1.5 g. (4.96 mmol.) under a nitrogen sparge to 50 ml. of a 1 M solution of BH_3·THF in dry tetrahydrofuran. The reaction mixture was left boiling for 12 hours. The reaction mixture was chilled in an ice bath and water was slowly added until the generation of hydrogen could no longer be observed. The solvent was removed on a rotary evaporator and the remaining solid was suspended in 50 ml. of 6 M hydrochloric acid. The reaction mixture was refluxed overnight. The volatiles were removed on a rotary evaporator. The excess of hydrochloric acid was eliminated by dissolving the remaining solid in water and by evaporating the solution under reduced pressure. This procedure had to be repeated three times. The solid residue obtained after the elimination of the hydrochloric acid in excess was dissolved in 30 ml. of water, and a concentrated solution of $LiOH·H_2O$ was added until the pH reached 12 - 13. The solution was extracted with 200 ml. of dichloromethane. The organic

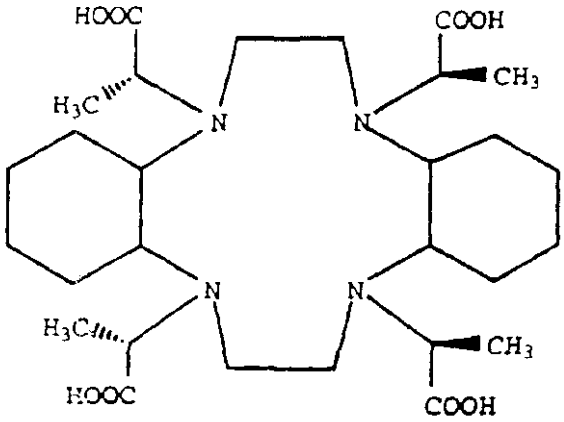
phase was separated by decantation and was dried (magnesium sulfate), filtered and evaporated to give 1.06 g. of a yellowish vitreous solid. An analytically pure sample was obtained by recrystallization of the tetraamine as the hydrochloride salt.

(C) 2,5,8,11-tetracarboxymethyl-14,15-benzo-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane

[0058] Bromoacetic acid (7.14 g., 51.4 mmol.) was dissolved in 20 ml. of water and was slowly neutralized by the dropwise addition of a solution of 2.05 g. (51.2 mmol.) of sodium hydroxide in 10 ml. of water while maintaining the temperature below 5° C. The reaction mixture was added to a solution of 2.35 g. (8.57 mmol.) of compound (B) in 10 ml. of water. The temperature was raised to 70 - 80° C. and the pH was maintained between 9 and 10 by the dropwise addition of an aqueous solution of sodium hydroxide (2.05 g., 51.42 mmol. in 10 ml. of water). The addition of sodium hydroxide was completed after 5 hours and the reaction mixture was left at 70 - 80° C. overnight. After cooling, the volume of the reaction mixture was reduced to 45 ml. on a rotary evaporator and a 6 M solution of hydrochloric acid was added dropwise until the pH was lowered to 3. A beige precipitate (3.5 g.) formed immediately. It was collected by filtration, recrystallized in water (colorless needles) and dried under vacuum. ^{13}C NMR (D_2O, strongly basic medium, ppm vs TMS): 182.2, 182.1, 161.9, 161.8, 140.9, 140.3, 129.9, 129.5, 128.8, 128.2, 64.0, 60.7, 59.9, 58.1, 57.3, 56.1, 55.1, 54.9, 51.0, 50.6, 50.4, 46,6, 28.4. Mass spectrum (FAB): m/e 507 (M+H).

Example 5

[0059]



Eicosahydrodibenzo[b,h][1,4,7,10]tetraazacyclo-dodecane-5,8,13,16-tetraacetic acid

(A) N,N'-(1,2-Cyclohexylene)-bis-(2-chloroacetamide)

[0060] A solution of 1,2-diaminocyclohexane (100 g., 0.88 mole) in methylene chloride (875 ml.) was cooled to 5° C. in an ice bath. The reaction mixture was treated concurrently with 1) a solution of chloroacetyl chloride (298 g., 2.64 mmol) in methylene chloride (1050 ml.), and 2) a solution of potassium carbonate (279 g., 2.02 mol.) in water (280 ml.), dropwise. After the addition was complete, the reaction mixture was stirred an additional 2 hours at ambient temperature. The reaction mixture was filtered. This reaction was repeated on the same scale. The solid remaining after filtration was combined with the above sample, and both were washed with 2 x 1000 ml. ice-cold water to afford 278 g. (60%) of compound (A) as a white solid.

(B) *Eicosahydrodibenzo[b,h][1,4,7,10]tetraazacyclo-dodecan-6,15-dione*

[0061] A solution of trans-1,2-diaminocyclohexane (15 ml., 125 mmol.) and compound (A) (33.4 g., 125 mmol.) in acetonitrile (3000 ml.) was treated with sodium carbonate (250 g., 2.36 mmol.) and the mixture was heated to reflux under nitrogen. The progress of the reaction was monitored by HPLC by noting the disappearance of starting materials along with the formation of a new peak corresponding to the desired product. The reaction was cooled to ambient temperature, and filtered to remove sodium carbonate. This solution was concentrated in vacuo to afford crude product

which was recrystallized from absolute ethanol to afford 9.2 g. (24%) of the trans-syn-trans isomer, compound (B), as a white solid with a melting point of 251 - 271° C.

(C) Eicosahydrodibenzo[b,h][1,4,7,10]tetraazacyclo-dodecane

[0062] A suspension of compound (B) (5.1 g., 16.5 mmol.) in freshly distilled tetrahydrofuran (250 ml.) was cooled to 0° C. under nitrogen, and treated dropwise with a solution of diborane in tetrahydrofuran (1 M, 132 ml., 132 mmol.). After the addition was complete, the reaction mixture was heated to reflux under nitrogen overnight. After 24 hours, the reaction mixture was cooled to 0° C., and the excess diborane was destroyed by the dropwise addition of 20% water in tetrahydrofuran (about 100 ml.). The solvent was removed in vacuo. The residue was treated with 132 ml. of 6 N hydrochloric acid, and heated to reflux overnight. The mixture was concentrated to dryness in vacuo. The residue was taken up in water and adjusted to pH 12.5 with concentrated sodium hydroxide. This material was extracted with methylene chloride and concentrated in vacuo to afford 3.4 g. (74%) of desired compound (C) as a white solid.

(D) (L)-Benzyl-2-Triflyloxypropionate

[0063] A solution of L-benzyl lactate (7.95 g., 44.1 mmol.) and pyridine (3.66 g., 46.3 mmol.) in methylene chloride (40 ml.) at 0° C. under nitrogen was treated with triflic anhydride (12.44 g., 44.1 mmol.) dropwise, via syringe. After 20 hours, silica gel TLC run in hexanes:methylene chloride (1:1, v/v) indicated formation of a single spot, as well as disappearance of the starting lactate. The pyridinium triflate was filtered, and the filtrate was concentrated in vacuo to afford crude product. This material was flashed on 200 g. of silica gel, eluting with hexanes: methylene chloride (2:1, v/v). The product-containing fractions were pooled to afford 5.4 g. (39%) of compound (D) as a colorless, light oil.

(E) Eicosahydrodibenzo[b,h][1,4,7,10]tetraazacyclo-dodecane-5,8,13,16-tetraacetic acid, tetrakis-5,8,13,16 (benzyloxycarbonyl)methyl ester

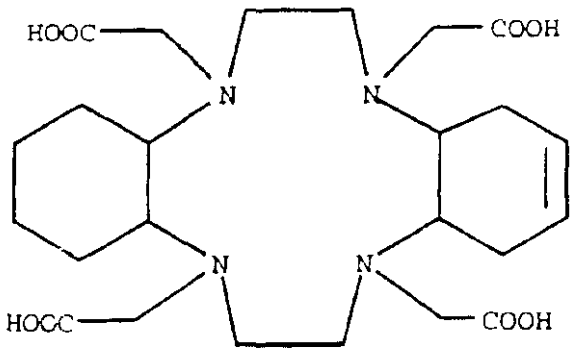
[0064] A solution of compound (C) (1.37 g., 4.91 mmol.) in acetonitrile (25 ml.) under nitrogen was treated with powdered potassium carbonate (3.38 g., 24.5 mmol.). The reaction mixture was treated with compound (D) (6.75 g., 21.6 mmol.), dropwise, via syringe. After 22 hours, the reaction mixture was diluted with 50 ml. of acetonitrile and filtered. The filtrate was concentrated in vacuo. The residue was suspended in 100 ml. of water, and extracted with 4 x 100 ml. of methylene chloride. The organic extracts were dried (magnesium sulfate) and concentrated in vacuo to afford 4.6 g. (101%) of product as a light, pale yellow oil. This material was flash chromatographed in 450 g. of silica gel, eluting with 4 liters of hexanes:ethyl acetate (3:1, v/v), followed by 2 liters of hexanes: ethyl acetate (1:1, v/v). The product-containing fractions were pooled to afford 1.62 g. (35%) of compound (E) as a viscous, pale yellow oil.

(F) Eicosahydrodibenzo[b,h][1,4,7,10]tetraazacyclo-dodecane-5,8,13,16-tetraacetic acid

[0065] A solution of compound (E) in methanol (6 ml.) and 2 M aqueous hydrochloric acid (2.5 ml.) was treated with 10% Pd/C (wet, Degussa type), and the reaction mixture was subjected to a steady stream of hydrogen gas at 1 atmosphere. After 22 hours, the reaction mixture was filtered through Celite® , and washed with 2 M aqueous hydrochloric acid. The filtrate was concentrated in vacuo and lyophilized from water to afford 870 mg. (73%) of ·4 hydrochloric acid salt. This mmaterial was combined with 75 mg. of previous crude product from an identical preparation, and the resulting solid was dissolved in 100 ml. of water. This solution was adjusted to pH 7.5 with concentrated ammonium hydroxide. The resulting solution was applied to a 2.5 x 45 cm column of AG1-X2 (formate form) anion exchange resin, and eluted with water to remove inorganic salts. The compound was eluted with a gradient from 2000 ml. of water to 2000 ml. of 0.2 N formic acid. Two separate fractions were collected and lyophilized: Fraction 1: 425 mg. (40% of theoretical), HPLC purity (see below) = 99.4%; Fraction 2: 100 mg. (10% of theoretical), HPLC purity = 94.8%.
HPLC: Retention time = 8.39 min., purity = 99.4%; Conditions: Column: PRP-X-100 5µ-100° A, 250 x 4.6 mm i.d.; Solvent: CH_3CN/50 mM phosphate buffer, pH 6.2 (1:4, v/v); Flow rate: 1.0 ml/minute; Detection: UV @ 220 nm.
IR: (KBr) 2942 and 2866 (CH stretching), 1723 and 1623 (C = O)cm^{-1}.
Mass Spectrum: (FAB) 569^+ $(M+H)^+$, 523^+ $(M+H\text{-}COOH)^+$, 497^+ $(M+H\text{-}CH(CH_3)COOH)^+$.
Anal. Calc'd. for $C_{28}H_{48}N_4O_8 \cdot 2.56$ water (614.8): C, 54.70; H, 8.71; N, 9.11; O, 27.48.
Found: C, 54.31; H, 8.94; N, 8.91.

Example 6

[0066]



1,2,3,4,4a,5,6,7,8,8a,9,12,12a,13,14,15,16,16a-Octadecahydrodibenzo[b,h][1,4,7,10]-tetraazacyclododecin-5,8,13,16-tetraacetic acid

(A) trans-4-Cyclohexene-1,2-diamine dihydrochloride

[0067] In an oven-dried 2-neck, round-bottomed flask equipped with a Dewar condenser and septum, a stirred solution of freshly distilled fumaryl dichloride (13.0 ml., 110 mmol.) in dry ethyl ether (50 ml.) was cooled to -50° C. under a dry nitrogen atmosphere. Condensed butadiene (40 ml.) was added via cannula to the solution, and the reaction mixture was allowed to warm to room temperature. The solution was allowed to reflux spontaneously for 3 hours, after which the excess butadiene and ethyl ether were removed in vacuo. The colorless oil was dissolved in dry 1,4-dioxane (50 ml.) and the solution was treated with azidotrimethylsilane (34 ml., 250 mmol.). Nitrogen evolution was initiated using an 80 - 85° C. oil bath and the reaction mixture was heated at 105° C overnight. The solution was cooled to room temperature, diluted with acetone (75 ml.), and cautiously treated with concentrated hydrochloric acid (35 ml.). The hydrochloric acid salt of the diamine was collected by filtration and was washed with acetone and ethyl ether. 14.4 g. (64.69%) of compound (A) was obtained as a white powder.

(B) N,N'-(1,2-Cyclohexylene)-bis-(2-chloroacetamide)

[0068] A solution of 1,2-diaminocyclohexane (50.0 g., 438 mmol.) in methylene chloride (438 ml.) was cooled to 0 - 5° C. and vigorously stirred with a mechanical stirrer. To it were concurrently added solutions of chloroacetyl chloride (105 ml., 1.28 mmol.) in methylene chloride (430 ml.) and potassium carbonate (139.5 g., 1.01 mol.) in water (279 ml.) over a period of 4 hours, and the resultant mixture was stirred at room temperature overnight. The suspension was filtered and the solid was thoroughly washed with ice-cold water to remove potassium carbonate. The layers in the filtrate were separated and the organic layer was concentrated to near dryness. The mixture was filtered and the solid was treated as before. The recovered solids were combined and dried in a vacuum oven at 50° C. over phosphorus pentoxide. The yield of compound (B) was 109.77 g. (93.84%) as a white solid.

(C) 1,2,3,4,4a,5,6,7,8,8a,9,12,12a,13,14,15,-16,16a-Octadecahydrodibenzo[b,h][1,4,7,10]-tetraaza-cyclododecin-6,15-dione

[0069] A suspension containg compound (B) (33.4 g., 125 mmol.), compound (A) (23.1 g., 125 mmol., hydrochloride salt) and anhydrous sodium carbonate (250 g., 2.36 mmol.) in acetonitrile (3750 ml.) was vigorously stirred and refluxed for 26 hours. After cooling, sodium carbonate was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The solid residue (22.1 g.) was recrystallized from ethanol (150 ml.) and afforded 7.95 g. of a material which contained two isomers. A single, pure isomer (1.28 g.) was obtained by a second recrystallization step. The original mother liquor furnished 1.97 g. more of the isomeric material. The mother liquor from the second crystallization was dried under vacuum and combined with the second crop of crystals. A portion of the material (3.22

g.) was purified by silica gel chromatography using methylene chloride:methanol (4:1 v/v) as the eluant to afford an additional 2.104 g. (65% recovery) of the pure product. The yield was 9.92 g. (26%) of the mixed isomer product.

(D) 1,2,3,4,4a,5,6,7,8,8a,9,12,12a,13,14,15,-16,16a-Octadecahydrodibenzo[b,h][1,4,7,10]-tetraazacyclo-dodecin-trihydrochloride .

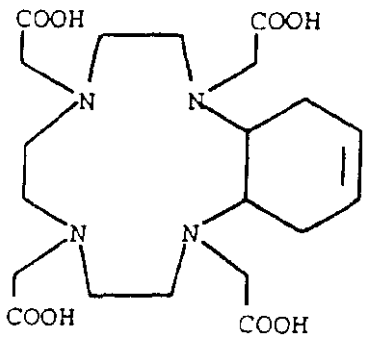
[0070] A mixture containing compound (C) (3.45 g., 11.3 mmol.) and 1 M LAH (40 ml.) in tetrahydrofuran (100 ml.) was refluxed for 21 hours under a dry nitrogen atmosphere. The solution was cooled and the excess LAH was decomposed by the careful addition of a saturated aqueous solution of Rochelles's salt (10 ml.). Absolute ethanol (50 ml.) was added to the suspension and the mixture was refluxed overnight. After filtration, the residual product in the filter cake was extracted by treatment of the solid with hot ethanol (2 x 100 ml.). The filtrates were combined and evaporated to afford 4.0 g. of a brownish mass. Crystallization from acetonitrile gave off-white crystals which dissolved in ethyl ether and hexane washes. A portion of this material (400 mg., 1.6 mmol.) was converted to the hydrochloride salt by treatment with methanolic hydrochloric acid (7 ml.).

(E) 1,2,3,4,4a,5,6,7,8,8a,9,12,12a,13,14,15,-16,16a-Octadecahydrodibenzo[b,h][1,4,7,10]-tetraazacyclodo-decin-5,8,13,16-tetraacetic acid

[0071] A mixture containing crude compound (D) (1.05 g., 3.77 mmol.), anhydrous potassium carbonate (2.61 g., 18.8 mmol.) and t-butyl bromoacetate (3.23 g., 16.6 mmol.) was heated at 50 - 55° C. overnight under a dry nitrogen atmosphere. After cooling, the reaction mixture was diluted with acetonitrile (10 ml.), filtered, and the filter cake was washed with an additional 10 ml. of acetonitrile. The filtrates were combined and evaporated under reduced pressure. The residue was suspended in water (25 ml.) and was extracted with methylene chloride (4 x 10 ml.). The organic layer was washed with brine (40 ml.), dried over magnesium sulfate, and evaporated to dryness to afford 2.35 g. of crude tetraester. Deprotection of the crude tetraester was accomplished by overnight treatment of the ester with anisole (12 ml.) and TFA (100 ml.) under a dry nitrogen atmosphere. The TFA was removed in vacuo and the residue was repeatedly dissolved in water and concentrated under reduced pressure until the solution was free of cloudiness. The crude product (2.0 g.) was dissolved in water (50 ml.), neutralized to pH 7.0 and purified by AG-1 (1.5 x 30 cm, formate) anion exchange chromatography. The column was washed with a linear gradient of formic acid (0 to 0.2 N formic acid, 2 l. each), and the product was eluted at approximately 0.05 N formic acid. The fractions containg pure product were combined, evaporated to dryness, dissolved in water and lyophilized to afford 541 mg. (45%) of the title compound as a fluffy white material.
HPLC:
Column: PRPX-100, 5µ, 250 x 4.6 mm.
Conditions: 20% CH_3CN in 50 mM NaH_2PO_4 (pH 6.2); flowrate: 1.0 ml./min.; detector: UV at 220 nm.; t_r = 7.31 minutes.
IR (KBr,cm^{-1}): 2940 (CH stretching); 1717 (C=O stretching); 1636 (C = C stretching).
MS(PPINCI NH_3/dep 100, m/z): 511 $(M + H)^+$.
Anal. calc'd. for $C_{24}H_{38}N_4O_8 \cdot 2.28\ H_2O$: C, 52.26; H, 7.78; N, 10.16; O, 29.81
Found: C, 52.27; H, 7.84; N, 10.01; H_2O. 7.44% (desorption KF).

Example 7

[0072]



2,5,8,11-Tetracarboxymethyl-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadec-14-ene

(A) 4,9-dioxo-2,5,8,11-tetraaza-bicyclo-[10,4,0]hexadec-14-ene

[0073] The synthesis of trans-4-cyclohexene-1,2-diamine has been reported by Witiak et al. (J. Med. Chem. 1987, 30, 1327-1336). Trans-4-cyclohexene-1,2-diamine (9.25 g., 82.5 mmol.) and N,N'-dichloroacethylenediamine (17.55 g., 82.5 mmol.) were dissolved in 2700 ml. of acetonitrile. Anhydrous sodium carbonate (158 g., 1.5 mol.) was added to the solution and the mixture was refluxed for 23 hours. After cooling, the insoluble salt was filtered off and the filtrate was brought to dryness. The solid residue was recrystallized in about 20 ml. of hot ethanol.
Melting point: 203-205°C.

(B) 2,5,8,11-bicyclo[10,4,0]hexadec-14-ene

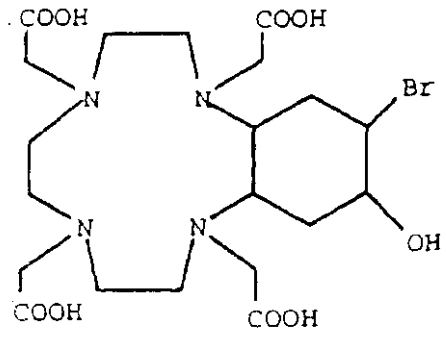
[0074] Compound (A) (0.8 g., 3.17 mmol.) was added under nitrogen to 100 ml. of diglyme that had been dried and distilled over lithium aluminum hydride. The compound solubilized when the temperature was increased. Lithium aluminum hydride (3.91 g., 0.1 mol.) was added to the warm solution and the temperature was brought to 100°C. The reaction mixture was agitated for 15 days. After cooling, excess hydride was destroyed by the careful addition of ethyl acetate and water. The insoluble material was filtered off and washed with water and ethanol. The solvents were eliminated under vacuum at 80°C. The residue was dissolved in hydrochloric acid 6 M and the solution was brought to dryness on a rotary evaporator. The residue was added to about 20 ml. of ethanol. The suspension was refluxed for one hour and then kept overnight at 4°C. The precipitate was filtered and dried under vacuum. The free amine was obtained by adding the hydrochloride to trichloromethane and saturated with dry ammonia. The suspension was agitated overnight and the insoluble ammonium chloride was filtered off. The solvent was eliminated and a viscous liquid remained. Mass spectrum: (FAB, sample in 3-nitrobenzyl alcohol): m/e 225 (M+H)

(C) 2,5,8,11-tetracarboxymethyl-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadec-14-ene

[0075] Bromoacetic acid (0.63 g., 4.5 mol.) was dissolved in water and was slowly neutralized below 5°C with an aqueous solution of sodium hydroxide (0.18 g., 4.55 mmol., in 2 ml. of water). This solution was added to a solution of compound (B) (0.17 g., 0.76 mmol.) in 3 ml. of water. The reaction mixture was heated at 70-80°C and a solution of sodium hydroxide (0.18 g., 4.55 mmol., in 2 ml. of water) was added dropwise over 5 hours so as to maintain the pH between 9 and 10. The agitation was continued overnight at 80°C. The pH was lowered to 3 with concentrated hydrochloric acid and the reaction mixture was slowly concentrated under a stream of air. The title compound easily formed crystals and was recrystallized in a small volume of water.
Yield: 45%, 0.15 g. ^{13}C NMR (in D_2O, protonated form): 177.6, 177.0, 173.0, 172.8, 127.5, 124.7, 64.5, 58.4, 57.3, 57.0, 55.7, 53.6, 52.5, 52.4, 50.2, 46.8, 47.6, 26.0, 25.4
Mass spectrum (sample in 3-nitrobenzyl alcohol): m/e 479 (M + Na), 501 (M - H + 2 Na).

Example 8

[0076]



2,5,8,11-Tetracarboxymethyl-16(14)-bromo-14(16)-hydroxy-2,5,8,11-tetraazabicyclo[10,4,0]hexadecane

[0077] The dihydrochloride of the compound of Example 7 (0.2 g., 0.38 mmol.) was dissolved in 4 ml. of water and the pH was adjusted to 6. N-bromosuccinimide (0.07 g., 0.38 mmol.) was added to this solution at 10°C. The reaction mixture was stirred at 10°C for one hour until N-bromosuccinimide was totally dissolved. The clear solution was kept overnight at 4°C. The solvent was stripped off in a rotary evaporator and in the dark. The solid residue was dissolved in a minimum amount of methanol, and acetone was added until the solution became slightly cloudy. The compound was left to crystallize overnight at 4°C, and was collected by filtration in the dark.
Yield: 45%. ^{13}C NMR (in D_2O, protonated form): 179.2, 178.6, 173.1, 172.5, 71.6, 63.2, 62.8, 58.5, 58.4, 57.2, 56.7, 56.0, 53.7, 52.9, 52.6, 51.7, 50.2, 49.4, 48.0, 47.7, 29.2, 28.9, 27.8, 27.1
Mass spectrum: (sample in 3-nitrobenzyl alcohol): m/e 575 and 577 (M + Na), 597 and 599 (M - H + 2 Na).

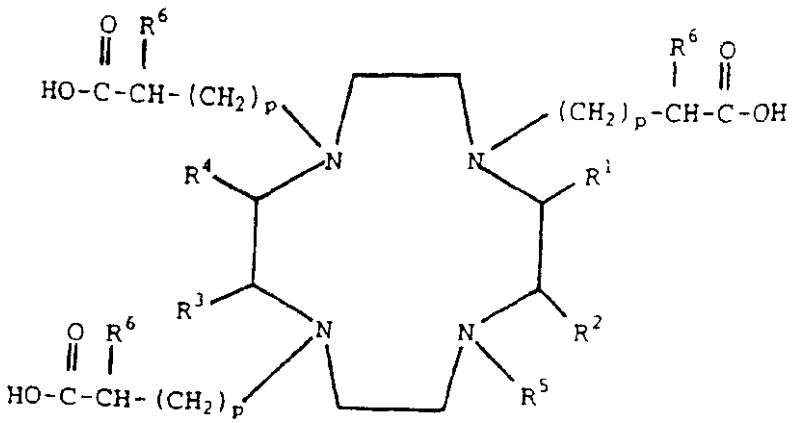
Example 9

Gadolinium (III) complexes of the ligands reported in Examples 1 - 8

[0078] All gadolinium (III) complexes were prepared by adjusting the pH of a stoichiometric mixture of gadolinium trichloride and one of the ligands reported in Examples 1 - 8 in water. The complexation reactions were started at about pH 3 and the solutions were heated to 60° C. for about 10 minutes before each addition of a few drops of a diluted aqueous solution of sodium hydroxide. The addition of sodium hydroxide was stopped when the pH reached 6.5. The complexation reactions were completed in a minimum of 3 to 4 hours. Each solution was concentrated and the products were purified by preparative HPLC. Evaporation of the appropriate fractions yielded colorless solids.

Claims

1. A compound of the formula:



wherein

R^1 and R^2 are both hydrogen and R^3 and R^4 together with the carbon atoms in the tetraazacyclododecane macrocycle to which they are attached form a fused fully or partially saturated non aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, straight or branched (C_1-C_5)alkyl, alkyl oxide of formula -R-OR wherein each R is a straight or branched (C_1-C_5)alkyl, hydroxy or hydroxyalkyl groups, and which may be further fused to a phenyl or cyclohexyl ring

R^5 is $-(CH_2)_p-CH(R^6)-C(=O)-OH$

p is 0 or 1 and R_6 is hydrogen or a straight or branched (C_1-C_5) alkyl group; or a salt thereof.

2. A compound of claim 1 selected from the group consisting of 2,5,8,11-Tetracarboxymethyl-2,5,8,11-tetraaza-bicyclo[10,4,0]hexadecane; 2,5,11-Tricarboxymethyl-8-(2'-hydroxyethyl)-2,5,8,11-tetraazabicyclo [10,4,0]hexadecane; 2,5,8,11-Tetracarboxymethyl-14,15-benzo-2,5,8,11-tetraazabicyclo[10,4,0]hexadecane; 2,5,8,11-Tetracarboxymethyl-2,5,8,11-tetraazabicyclo[10,4,0]hexadec-14-ene; and 2,5,8,11-Tetracarboxymethyl-16(14)-bromo-14 (16)-hydroxy-2,5,8,11-tetraazabicyclo[10,4,0]hexadecane.

3. A metal chelate comprising a compound of Claim 1 complexed with a metal atom.

4. The chelate of Claim 3 wherein the metal is selected from atoms having an atomic number of 21 to 29, 42, 44, or 57 to 83.

5. The chelate of Claim 4 wherein said metal is gadolinium.

6. A pharmaceutical composition comprising a compound of any of the preceding claims and a pharmaceutically acceptable vehicle or diluent.

7. A diagnostic pharmaceutical composition comprising at least a compound of claim 3, 4, or 5.

8. Use of a compound of claims 3,4, or 5 for the preparation of a diagnostic formulation for obtaining images of organs and/or tissues of human or animal bodies, by the application of magnetic resonance imaging.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 12 7327

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	EP 0 073 456 A (ASAHI KASEI KOGYO KABUSHIKI KAISHA) 9 March 1983 (1983-03-09) *Page 107-111: claims*	1	C07D257/10 A61K49/00
A	EP 0 108 181 A (CIBA-GEIGY AG) 16 May 1984 (1984-05-16) *Page 4: claims*	1	
A	EP 0 162 804 A (CIBA-GEIGY AG) 27 November 1985 (1985-11-27) *Page 11-13: claims*	1	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)
C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	8 January 2002	Chouly, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 12 7327

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

08-01-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0073456 A	09-03-1983	JP 1013478 B	06-03-1989
		JP 1525794 C	30-10-1989
		JP 58032891 A	25-02-1983
		JP 1432105 C	24-03-1988
		JP 58038297 A	05-03-1983
		JP 62041675 B	03-09-1987
		JP 58038298 A	05-03-1983
		DE 3267697 D1	09-01-1986
		EP 0073456 A1	09-03-1983
		US 4465630 A	14-08-1984
EP 0108181 A	16-05-1984	EP 0108181 A1	16-05-1984
		DE 3276165 D1	04-06-1987
EP 0162804 A	27-11-1985	DE 3562917 D1	30-06-1988
		EP 0162804 A1	27-11-1985
		JP 60248695 A	09-12-1985

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

肝膽磁性共振對比劑

一種通式化合物：

其中：R1 和 R2 爲氫，而 R3 和 R4 與四氮雜環十二烷的碳原子大環合，它們彼此相連形成一完全或者部分飽和的非芳香環己基環，該環可以被一個或者多個滷素，直鏈或者支鏈（C1 - C5）的烷基，分子式爲 -R-OR 的烷氧基取代或不取代，其中，每一個 R 是支鏈或支鏈的（C1 - C5）的烷基，羥基或羥烷基，而且可以進一步融合成苯或已環，而 p 是 0，R6 爲氫或者直鏈或支鏈（C1 - C5）的烷基；或其鹽和金屬螯合物，特別是釓的螯合物，含有該化合物的藥物和診斷組合物以及它們在 MRI 中的應用。