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(54) Title: NOVEL COMPOSITIONS FOR MAGNETIC RESONANCE IMAGING

(57) Abstract

Methods and compositions for enhancing magnetic resonance imaging in at least a portion of a warm-blooded animal.

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NOVEL COMPOSITIONS FOR MAGNETIC RESONANCE IMAGING

Background of the Invention

This invention relates to magnetic resonance imaging agents, and more particularly to methods and compositions for enhancing magnetic resonance imaging.

The recently developed technique of magnetic resonance imaging (MRI) encompasses the detection of certain atomic nuclei utilizing magnetic fields and radio-frequency radiation. It is similar in some respects to X-ray computed tomography (CT) in providing a cross-sectional display of the body organ anatomy with excellent resolution of soft tissue detail. As currently used, the images produced constitute a map of the distribution density of protons and/or the relaxation times in organs and tissues. The technique of MRI is advantageously non-invasive as it avoids the use of ionizing radiation.

While the phenomenon of MRI was discovered in 1945, it is only relatively recently that it has found application as a means of mapping the internal structure of the body as a result of the original suggestion of Lauterbur (Nature, 242, 190-191 (1973)). The fundamental lack of any known hazard associated with the level of the magnetic and radio-frequency fields that are employed renders it possible to make repeated scans on vulnerable individuals. Additionally, any scan plane can readily be selected, including transverse, coronal and sagittal sections.

In an MRI experiment, the nuclei under study in a sample (e.g. protons) are irradiated with the appropriate

radio-frequency (RF) energy in a controlled gradient magnetic field. These nuclei, as they relax, subsequently emit RF energy at a sharp resonance frequency. The resonance frequency of the nuclei depends on the applied magnetic field.

According to known principles, nuclei with appropriate spin when placed in an applied magnetic field (B, expressed generally in units of gauss or Tesla (10^4 gauss)) align in the direction of the field. In the case of protons, these nuclei precess at a frequency, F, of 42.6 MHz at a field strength of 1 Tesla. At this frequency, an RF pulse of radiation will excite the nuclei and can be considered to tip the net magnetization out of the field direction, the extend of this rotation being determined by the pulse, duration and energy. After the RF pulse, the nuclei "relax" or return to equilibrium with the magnetic field, emitting radiation at the resonant frequency. The decay of the emitted radiation is characterized by two relaxation times, i.e., T_1, the spin-lattice relaxation time or longitudinal relaxation time, that is, the time taken by the nuclei to return to equilibrium along the direction of the externally applied magnetic field, and T_2, the spin-spin relaxation time associated with the dephasing of the initially coherent precession of individual proton spins. These relaxation times have been established for various fluids, organs and tissues in different species of mammals.

In MRI, scanning planes and sliced thicknesses can be selected. This selection permits high quality transverse, coronal and sagittal images to be obtained directly. The absence of any moving parts in MRI equipment promotes a high reliability. It is believed that MRI has a greater potential than CT for the selective examination of tissue characteristics. The reason for this being that

in CT, X-ray attenuation and coefficients alone determine image contrast, whereas at least four separate variables (T_1, T_2, proton density and flow) may contribute to the MRI signal. For example, it has been shown (Damadian, Science, 171, 1151 (1971)) that the values of the T_1 and T_2 relaxation in tissues are generally longer by about a factor of two (2) in excised specimens of neoplastic tissue compared with the host tissue.

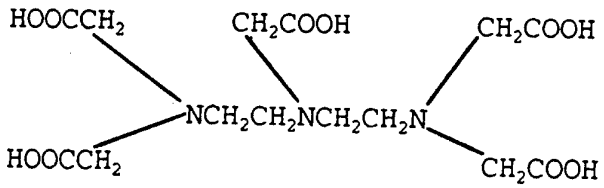
By reason of its sensitivity to subtle physiochemical differences between organs and/or tissues, it is believed that MRI may be capable of differentiating different tissue types and in detecting diseases which induce physicochemical changes that may not be detected by X-Ray or CT which are only sensitive to differences in the electron density of tissue.

As noted above, two of the principal imaging parameters are the relaxation times, T_1 and T_2. For protons (or other appropriate nuclei), these relaxation times are influenced by the environment of the nuclei (e.g., viscosity, temperature, and the like). These two relaxation phenomena are essentially mechanisms whereby the initially imparted radio-frequency energy is dissipated to the surrounding environment. The rate of this energy loss or relaxation can be influenced by certain other nuclei which are paramagnetic. Chemical compounds incorporating these paramagnetic nuclei may substantially alter the T_1 and T_2 values for nearby protons. The extent of the paramagnetic effect of the given chemical compound is a function of the environment within which it finds itself.

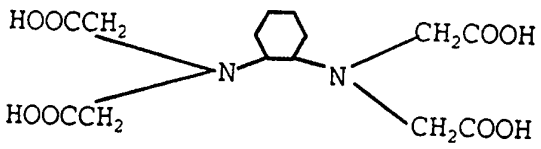
In general, paramagnetic ions of elements with an atomic number of 21 to 29, 42 to 44 and 58 to 70 have been found effective as MRI contrasting agents. Suitable such

ions include chromium (III), manganese (II), manganese (III), iron (III), iron (II), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III) and ytterbium (III). Because of their very strong magnetic moments, gadolinium (III), terbium (III), dysprosium (III), holmium (III) and erbium (III) are preferred. Gadolinium (III) ions have been particularly preferred as MRI contrasting agents.

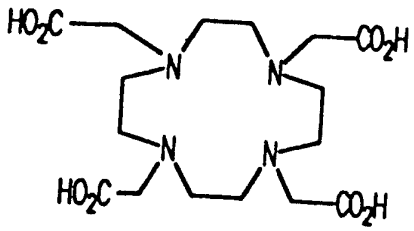
Typically, the divalent and trivalent paramagnetic ions have been administered in the form of complexes with organic complexing agents. Such complexes provide the paramagnetic ions in a soluble, non-toxic form, and facilitate their rapid clearance from the body following the imaging procedure. Gries, et al., U.S. Patent 4,647,447, disclosed complexes of various paramagnetic ions with conventional aminocarboxylic acid complexing agents. A preferred complex disclosed by Gries, et al., is a complex of gadolinium (III) with diethylenetriaminepentaacetic acid ("DTPA"). DTPA is represented by the formula:



Paramagnetic ions, such as gadolinium (III), have been found to form strong complexes with other polyamino-carboxylic acids such as, cyclohexanediaminetetraacetic acid ("CDTA") represented by the formula:



and tetraazacyclododecane-N,N',N",N'"-tetraacetic acid ("DOTA") represented by the formula:



These complexes do not dissociate substantially in physiological aqueous fluids. The complexes have a net charge of -1 or -2, and generally are administered as soluble salts. Typical such salts are the sodium and N-methylglucamine salts.

The administration of ionizable salts is attended by certain disadvantages. These salts can raise the in vivo ion concentration and cause localized disturbances in osmolality, which in turn, can lead to edema and other undesirable reactions.

Efforts have been made to design non-ionic paramagnetic ion complexes. In general, this goal has been achieved by converting one or more of the free carboxylic acid groups of the polyamino acid type ligands such as EDTA or DTPA to neutral, non-ionizable groups. For example, S. C. Quay, in U.S. Patents 4,687,658 and 4,687,659, discloses alkylester and alkylamide derivatives respectively, of DTPA complexes. Similarly, published Dean et al., U.S. Patent

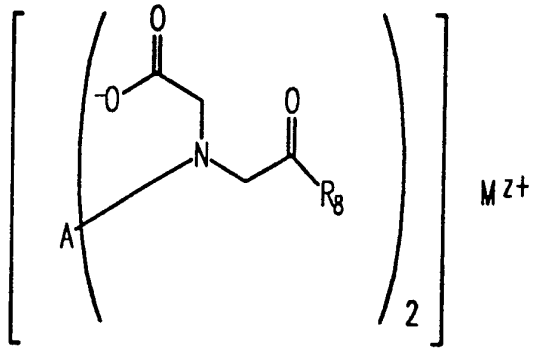
4,826,673 discloses mono- and polyhydroxyalkylamide derivatives of DTPA and their use as complexing agents for paramagnetic ions.

The nature of the derivative used to convert carboxylic acid groups to non-ionic groups can have a significant impact on solubility. For example, derivatizing the carboxylic acid groups with hydrophobic alkylamide groups substantially decreases the water solubility of the complex. The solubility of the complex in physiological fluids can, in turn, affect the tissue selectivity of the complex. Hydrophilic complexes tend to concentrate in the interstitial fluids, whereas hydrophobic complexes tend to associate with cells. Thus, differences in hydrophilicity can lead to different applications of the compounds. See, for example, Weinmann, et al., AJR, 142, 679 (Mar. 1984) and Brasch, et al., AJR, 142, 625 (Mar. 1984).

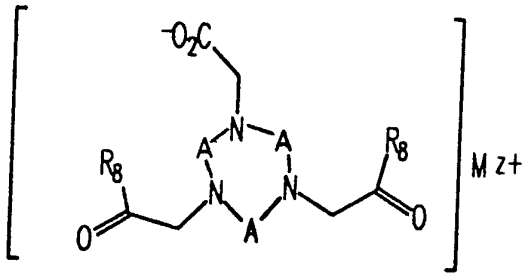
Thus, a need continues to exist for new and structurally diverse ionic and non-ionic complexes of paramagnetic ions for use as MRI agents. A further need also exists in the art to develop highly stable complexes with good relaxivity and low osmolar characteristics.

Summary of the Invention

The present invention provides novel complexing agents and complexes of complexing agents with paramagnetic ions for use in MRI. The complexes are represented by the two following general formulas:



Formula I

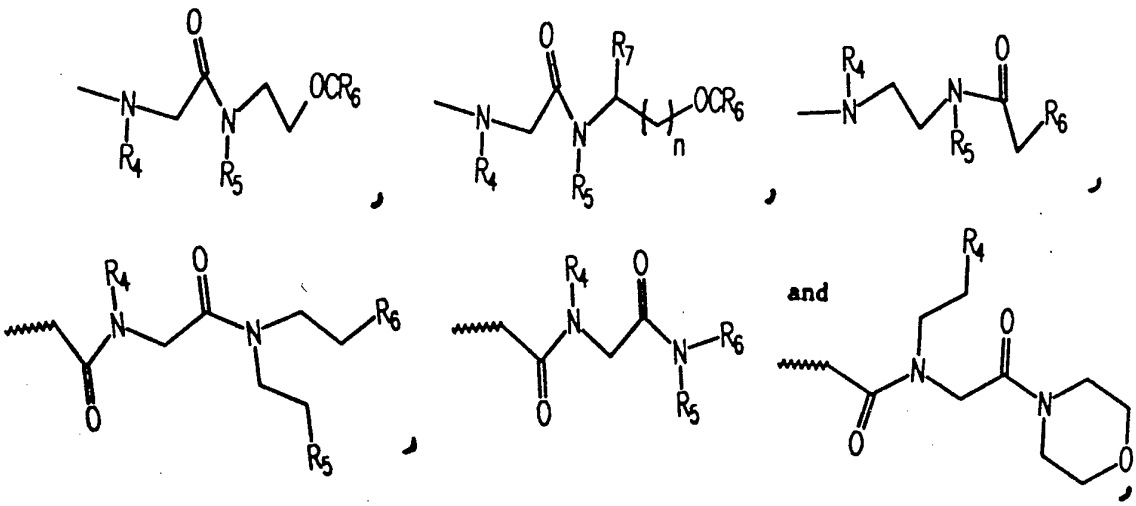


Formula II

wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5COCH_2R_6$, $-(CH_2)_nCONR_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $-(CH_2)_nCONR_4(CH_2)_nCH_2CON\langle\rangle O$, and $-(CH_2)_nCONR_1(CH_2)_nCONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl -such as for example methyl or ethyl wherein methyl is preferable to minimize lipophilicity, C_{1-8} alkoxy -such as for example methoxy or ethoxy, C_{1-8} mono- or poly-hydroxyalkyl -such as for example hydroxymethyl or dihydroxypropyl wherein dihydroxypropyl is preferred to enhance water solubility, C_{1-8} alkylalkoxy -such as for

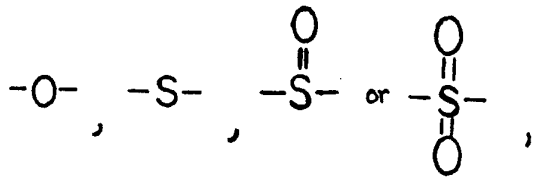
example methylmethoxy, C_{1-8} alkoxyalkyl - such as for example methoxymethyl or methoxyethyl wherein methoxymethyl is preferred to reduce lipophilicity, and C_{5-8}aryl - such as for example phenyl or benzyl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a hydrocarbon ring of 5, 6 or 7 members.

Examples of possible R_8 substituents include but are not limited to:



wherein the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl -such as for example methyl or ethyl wherein methyl is preferable to minimize lipophilicity, hydroxy, C_{1-8} alkoxy -such as for example methoxy or ethoxy, C_{1-8} mono- or poly- hydroxyalkyl -such as for example hydroxymethyl or dihydroxypropyl wherein dihydroxypropyl is preferred to enhance water solubility, C_{1-8} alkoxyalkyl -such as for example methoxymethyl or methoxyethyl wherein methoxymethyl

is preferred to reduce lipophilicity, C_{1-8} aminoalkyl -such as for example aminomethyl, C_{5-10} aryl -such as for example phenyl or benzyl, C_{5-10} substituted aryl -such as for example aminophenyl or iodophenyl and C_{1-12} acylaminoalkyl -such as for example acetylaminomethyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl -such as for example methyl or ethyl wherein methyl is preferable to reduce lipophilicty, C_{5-10} aryl -such as for example phenyl or benzyl, C_{5-10} aminoaryl -such as for example aminophenyl or aminobenzyl, hydroxy, C_{1-8} alkoxy -such as for example methoxy or ethoxy, C_{1-8} mono- or poly- hydroxyalkyl -such as for example hydroxymethyl or hydroxyethyl, C_{1-8} alkoxyalkyl -such as for example methoxymethyl or methoxyethyl, C_{1-8} aminoalkyl -such as for example aminomethyl or aminoethyl, carbamoyl and C_{1-12} acylaminoalkyl -such as for example acetylaminomethyl or propanoylaminomethyl; n is an integer between 0 and 10; M^{z+} is a paramagnetic ion of an element with an atomic number of 21-29, 42-44 or 58-79, and a valence Z of 2+, 3+ or 4+; (Z-r) of all the R_8 groups are $-O^-$ and r is equal to 0, 1, 2, 3 or 4.

According to the present invention in cases where M^{z+} is a heavy metal ion, such complexes can be used as X-ray contrast agents; if M^{z+} is a radioactive isotope the

complexes may be used as diagnostic or therapeutic agents in nuclear medicine.

The compounds of the present invention may also be attached to a biomolecule or polymeric compound. Examples of such compounds include biomolecules such as hormones, proteins, lipids, albumins, polyhydroxyl compounds such as amino sugars, carbohydrates and polylysines to name a few. The compounds of the present invention are attached to such a polymeric compound through the carboxyl group of the complexing acid or by other conventional methods.

The compounds of the present invention may also be carried by liposomes such as unilamellar or multilamellar vesicles and by other drug delivery systems.

Also, disclosed is a diagnostic composition and a method of performing a diagnostic procedure which involves administering to a warm-blooded animal an effective amount of the above-described complex and then exposing the warm-blooded animal to a diagnostic procedure, thereby imaging at least a portion of the body of the warm-blooded animal.

Detailed Description of the Invention

The complexing agents employed in this invention are derivatives of the well-known chelating agents such as DTPA, EDTA, CDTA or DOTA. In these derivatives, one or more of the carboxylic acid groups are converted to amide groups. Thus, for example, if the paramagnetic ion is trivalent, one or two of the carboxylic acid groups of DTPA may be derivatized to the amide form. Likewise, if the

paramagnetic ion is divalent, one to three of the carboxylic acid groups of DTPA may be derivatized to the amide form. The same principle would be true if derivatives of other chelating agents such as EDTA, CDTA or DOTA were to be used.

The amide derivatives of chelating agents such as DTPA, EDTA, CDTA or DOTA are prepared in a conventional manner. In general, they are prepared by reacting a stoichiometric amount of a desired amine with a reactive derivative of a chelating agent under amide-forming conditions. Such reactive derivatives include, for example, anhydrides, mixed anhydrides and acid chlorides.

In one embodiment, the reactions are conducted in an organic solvent at an elevated temperature. Suitable solvents include those in which the reactants are sufficiently soluble and which are substantially unreactive with the reactants and products. Lower aliphatic alcohols, ketone, ethers, esters, chlorinated hydrocarbons, toluene, xylene, lower aliphatic hydrocarbons, and the like may be advantageously used as reaction solvents. Examples of such solvents are methanol, ethanol, 2-propanol, 2-butanol, acetone, methylethylketone, diethylketone, methylacetate, ethylacetate, chloroform, methylenechloride, dichloroethane, hexane, heptane, octane, decane, and the like. If an acid chloride is used as a starting material, then the reaction solvent advantageously is one which does not contain reactive functional groups, such as hydroxyl groups, as these solvents can react with the acid chlorides, thus producing unwanted byproducts.

The reaction temperature may vary widely, depending upon the starting materials employed, the nature of the reaction solvent and other reaction conditions.

Such reaction temperatures may range, for example, from about 0°C to about 150°C preferably from about 30°C to about 70°C.

Following the reaction of the reactive derivative with the amine, any remaining anhydride or acid chloride groups can be hydrolyzed to the carboxylic groups by adding a stoichiometric excess of water to the reaction mixture and heating for a short time.

The resulting DTPA, EDTA, CDTA or DOTA amide is recovered from the reaction mixture by conventional procedures. For example, the product may be precipitated by adding a precipitating solvent to the reaction mixture and recovered by filtration or centrifugation.

The paramagnetic ion is then combined with the above isolated amide derivative under complex-forming conditions. In general, any of the paramagnetic ions referred to above can be employed in making the complexes of this invention. The complexes can conveniently be prepared by mixing a suitable oxide or salt to the paramagnetic ion with the complexing agent in aqueous solution. To assure complete complex formation, a slight stoichiometric excess of the complexing agent may be used. In addition, an elevated temperature, e.g., ranging from about 20°C to about 100°C, preferably from about 40°C to about 80°C, may be employed to insure complete complex formation. Generally, complete complex formation will occur within a period from a few minutes to a few hours after mixing. The complex may be recovered by precipitation using a precipitating solvent such as acetone, and further purified by crystallization, if desired.

The novel complexes of this invention can be formulated into diagnostic compositions for enteral or parenteral administration. These compositions contain an effective amount of the paramagnetic ion complex along with conventional pharmaceutical carriers and excipients appropriate for the type of administration contemplated. For example, parenteral formulation advantageously contain a sterile aqueous solution or suspension of from about 0.05 to 1.0M of a paramagnetic ion complex according to this invention. Preferred parental formulations have a concentration of paramagnetic ion complex of 0.1M to 0.5M. Such solutions also may contain pharmaceutically acceptable buffers and, optionally, electrolytes such as sodium chloride. Advantageously, the compositions may further contain physiologically acceptable non-toxic cations in the form of suitable organic or inorganic salts, including suitable soluble complex salts with a chelate/ligand to enhance safety. Such chelates/ligands include the ligands set forth above used to complex paramagnetic and/or heavy metals to provide the complex formulations of this invention. Advantageously, the cation-ligand complex salt is provided in amounts ranging from about 0.001 Mol percent to about 15 Mol percent excess, of the ligand-metal complex. Examples of such physiologically acceptable non-toxic cations include sodium ions, calcium ions, magnesium ions, copper ions, zinc ions and the like including mixtures thereto. Calcium ions are preferred.

Parenteral compositions may be injected directly or mixed with a large volume parenteral composition for systemic administration.

Formulations for enteral administration may vary widely, as is well-known in the art. In general, such formulations are ligands which include an effective amount

of the paramagnetic ion complex in aqueous solution or suspension. Such enteral compositions may optionally include buffers, surfactants, thixotropic agents, and the like. Compositions for oral administration may also contain flavoring agents and other ingredients for enhancing their organoleptic qualities.

The diagnostic compositions are administered in doses effective to achieve the desired enhancement of the MR image. Such doses may vary widely, depending upon the particular paramagnetic ion complex employed, the organs or tissues which are the subject of the imaging procedure, the MR imaging equipment being used, etc. In general, parenteral dosages will range from about 0.01 to about 1.0 MMol of paramagnetic ion complex per kilogram of patient body weight. Preferred parenteral dosage range from about 0.05 to about 0.5 MMol of the paramagnetic ion complex per kilogram of patient body weight. Enteral dosages generally range from about 0.5 to about 100 MMol, preferably from about 1.0 to about 20 MMol of paramagnetic ion complex per kilogram of patient body weight.

The novel MRI contrasting agents of this invention possess a unique combination of desirable features. The paramagnetic ion complexes exhibit a high solubility in physiological fluids, notwithstanding in some cases their substantially non-ionic character. This high solubility allows the preparation of concentrated solutions, thus minimizing the amount of fluid required to be administered. In selected cases the non-ionic character of the complex also reduces the osmolality of the diagnostic compositions, thus preventing undesired edema and other side effects.

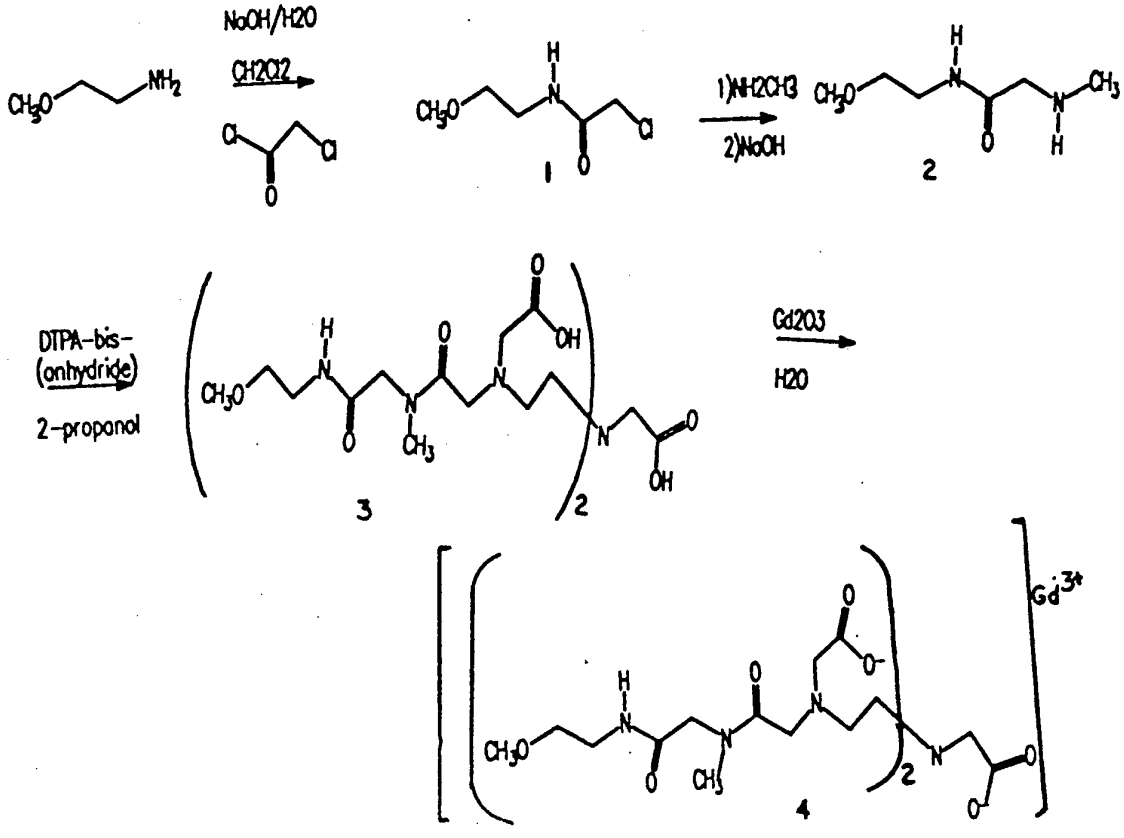
The diagnostic compositions of this invention are

used in the conventional manner. Compositions may be administered in a sufficient amount to provide adequate visualization, to a warm-blooded animal either systemically or locally to an organ or tissues to be imaged, and the animal then subjected to the MRI procedure. The compositions have been found to enhance the magnetic resonance images obtained by these procedures. In addition to their utility and magnetic resonance imaging procedures, the complexing agents of this invention may also be employed for delivery of radiopharmaceuticals or heavy metals for X-Ray contrast into the body. The invention is further illustrated by the following examples, which are not intended to be limiting.

EXAMPLE 1

Preparation of

{Aqua(N,N"-bis(N^{1111}-2-methoxyethylcarbamoyl-methyl-N^{111}-methylcarbamoylmethyl)diethylene-triamine-N,N',N"-triacetate)}gadolinium(III) (4)



The first step is a modified Schotten-Baumann acetylation of 2-methoxy-ethyl amine. The chloroamide, 1, is readily purified by vacuum distillation (1 torr, 58°C). Next, methylamine is N-alkylated with the chloroamide. The resulting N-methylglycine(2-methoxyethylamide), 2, is also purified by vacuum distillation (1 torr, 28°C). Reaction of the glycinamide with diethylenetriaminepentaacetic dianhydride in 2-propanol gives the desired bis(amide) of DTPA, 3. Complexation of the ligand with gadolinium gives the complex, 4. The complex is purified by reverse phase flash chromatography.

Experimental:

A) Chloro(N-(2-methoxyethyl))acetamide, (1)

In a three-necked 2L round bottom flask fitted with two 500mL addition funnels, containing 56.4g (39.8mL, 0.50mole) chloroacetyl chloride in 400mL dichloromethane and 20g (0.50mole) sodium hydroxide in 400mL water, respectively, and a water-cooled condenser, was placed 35.7g (41.3mL, 0.48mole) 2-methoxyethylamine, 100mL water, 100mL dichloro-methane. The reaction vessel was cooled to 0°C by a salt-ice bath. The organic and aqueous solutions were allowed to add slowly, ~0.25mL per minute, to the reaction mixture. During the addition the pH of the water phase of the reaction was monitored and the rate of addition of the alkali solution adjusted so as to maintain pH=12. When the addition was complete, the mixture was allowed to warm to room temperature and stir overnight. The organic layer was removed by siphon and dried with magnesium sulfate for four hours. The mixture was filtered through #4 filter paper on a large Buchner funnel and the sulfate washed with 2x100mL fresh dichloromethane. The

combined filtrates were then placed in 2L round bottomed flask and the mixture distilled at 1 torr. Fractions collected from 55°C to 60°C were combined and analyzed by NMR. Yield 31.1g (43% based on starting 2-methoxyethylamine). TLC (silica on glass, 2% methanol in dichloromethane) R_f=0.40. $^1H(\delta, CDCl_3)$ 3.28(s,3H), 3.40(m,4H), 3.97(s,2H), 6.92(br, 1H). $^{13}C\{^1H\}$ (δ, $CDCl_3$) 39.27, 42.32, 58.60, 70.54, 166.22.

B) N'-(2-methoxyethyl)-N-methylglycinamide, (2)

To a 1L round bottom flask, fitted with reflux condenser and charged with 500mL 40% w/w aqueous methylamine, was added, with stirring, 31.1g (0.21mole) chloroamide, 1. The mixture was heated to 35°C and stirred overnight. To the mixture was added 8.8g (0.22mole) sodium hydroxide. The mixture was distilled at room pressure and the fraction boiling from 89°C to 98°C. The crude distillate was dried with magnesium sulfate and distilled again giving a clear colorless oil. Yield 13.9g (45% based on starting chloroamide, 1). TLC (silica on glass, 15% concentrated ammonium hydroxide in methanol) R_f=0.35. $^1H(\delta, CDCl_3)$ 1.38(br, 1H), 2.32(s,3H), 3.14(s,2H), 3.26(s,3H), 3.37(m,4H), 7.35(br,1H). $^{13}C\{^1H\}(\delta,CDCl_3)$ 36.28, 38.39, 54.24, 58.53, 71.13, 171.62.

C) N,N"-bis(N""-2-methoxyethylcarbamoylmethyl-N"'-methylcarbamoylmethyl)diethylenetriamine-N,N',N"-triacetic acid, (3)

A 2L round bottom flask was charged with 13.9g (0.095mole) glycinamide, 2, 17.0g (0.047mole) diethylenetriaminepentaacetic dianhydride and 1L 2-propanol. The mixture was heated to 60°C and allowed to stir overnight. The mixture was cooled to room temperature, transferred, in 1L lots, to a 2L recovery flask and the solvent removed by means of a rotary-

evaporater (water aspirator). To residue was added 10L distilled/deionized water, and the mixture filtered to remove diethylenetriaminepentaacetic acid. The water was removed by rotary evaporation giving an orange glass. Yield 34g (100%=30.9g based on starting anhydride). Typically, the ligand is used "as is" for complexometric reactions. A small sample was purified by reverse phase flash column chromatography. IR(cm^{-1}) C-O 1724 (m,sh), 1659 (vs,). Anal. Calc. %C 48.07, %H 7.29, %N 15.09. Found %C 47.77, %H 7.04, %N 15.39.

D) {Aqua(N,N"-bis(N""-2-methoxyethylcarbamoylmethyl-N"'-methylcarbamoylmethyl)diethylenetriamine-N,N',N"-triacetate)}gadolinium(III), (4)

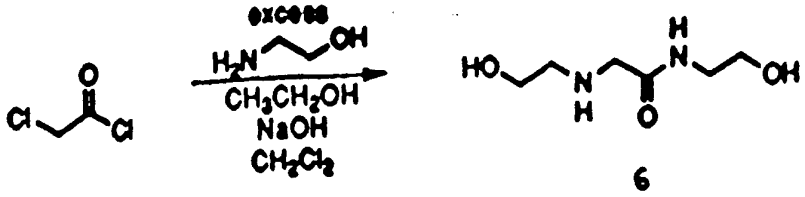
A 1L round bottom flask was charged with 34g (assuming 30.9g, 0.048mole anhydrous ligand present) crude ligand, 3, 8.6g (0.024mole) gadolinium oxide and 500mL water. The mixture was heated to gentle reflux and stirred overnight. The slightly turbid yellow mixture was filtered (0.42 micron) and concentrated to 50mL by rotary evaporator with a water aspirator. The thick clear solution was applied to a 5x35cm column loaded with YMC C-18 reverse phase packing. The column was eluted with water. Those fractions containing >98% pure complex, by HPLC with uv detector at 215nm, were combined, concentrated, filtered (0.42 micron) and evaporated to give a clear, colorless powder. Yield 20.5g (50% based on starting ligand, 3.) IR (cm^{-1}) C=O 1676 (s,sh), 1620 (vs). Anal. Calc. for $C_{26}H_{46}N_7O_{12}\cdot 3H_2O$ %C 36.31, %H 6.09, %N 11.40, %Gd 18.29. Found %C 36.04, %H 5.90, %N 11.12, %Gd 17.79. Karl Fisher water calc. 5.91%, found 6.30%.

The mouse i.v. LD_{50} value of a 0.5M solution of {Aqua(N,N"-bis(N""-2-methoxyethylcarbamoylmethyl-N'"-methylcarbamoylmethyl)diethylenetriamine-N,N',N"-triacetate)}gadolinium(III) was determined to be 32.5

mmol/kg (confidence limit of 27.3 - 38.8 mmol/kg) and the relaxivity rates ($mmol^{-1}sec^{-1}$) were obtained using the Bruker NMR Minispec (20 MHz) spectrometer at 40°C in both sterile water for injection (SWFI) and 4% bovine serum albumin (BSA): R_1: SWFI, 4.3; BSA, 4.6; R_2: SWFI, 4.1; BSA, 5.3.

EXAMPLE 2

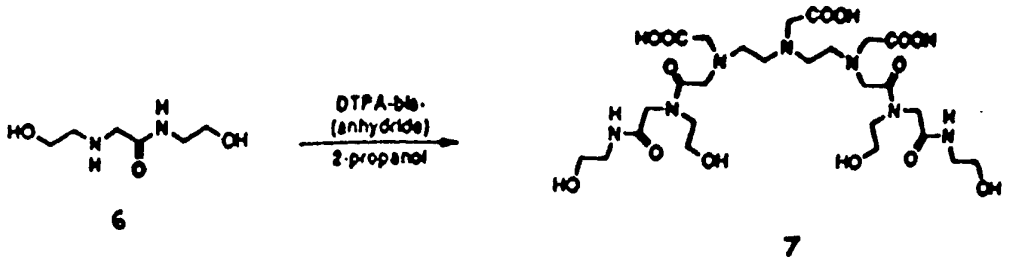
A) N'-(2-Hydroxyethyl)-N-(2-hydroxyethyl)glycinamide(6)



6

Chloroacetyl chloride (56.7 g, 0.5 mol) was added dropwise to ethanolamine (160 g, 2.6 mol) in methylene chloride (150 ml) at ice water temperature and the mixture was allowed to stir at this temperature for 60 minutes and then at room temperature for 60 minutes. The solvent was removed by rotary evaporation. Ethanol (150 ml) was used to dissolve the residue. Sodium hydroxide pellets (40.0 g, 1.0 mol) were added to the mixture. The mixture was stirred at room temperature for 2 hours. Sodium chloride was removed by filtration. The filtrate was rotary evaporated under reduced pressure (<0.5 torr) to remove the ethanol, water, and ethanolamine. The crude product (72.3 g, 89%) was purified by C-18 chromatography using deionized water for elution. After the water was removed, the purified product was a colorless liquid: ^{1}H NMR δ 2.7-2.8 (m, 2H), 3.3-3.5 (m, 4H), and 3.6-3.8 (m, 4H); C-13 NMR δ 177.6 (C=O), and 44.2, 52.9, 54.0, 63.0, and 63.4 representing 4 carbon atoms on two hydroxyethyl moieties and 1 methylene carbon atom on glycine moiety.

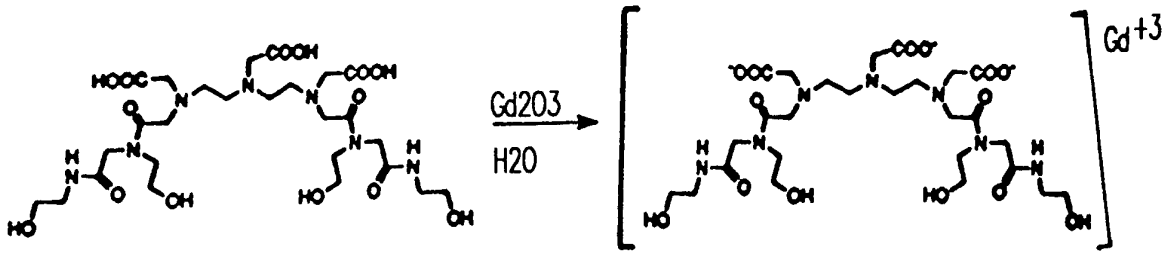
B) N,N"-bis[N""-(2-hydroxyethyl)carbamoylmethyl-N'"-(2-hydroxyethyl)carbamoylmethyl]diethylenetriamine-N,N',N"-triacetic acid(7)



6 7

A slurry of 4.64 g (13.0 m mol) DTPA bisanhydride in 20 ml dry dimethyl formamide (DMF) was prepared. A solution of 4.0 g (24.7 m mol) of the secondary amine (6) in 15 ml dry DMF was added dropwise to it. The mixture was stirred at room temperature for 60 minutes and then at 55°C for 2 hours. At the end of the reaction, 5 ml of water was added in order to digest the unreacted DTPA bisanhydride. The entire mixture was stirred at room temperature overnight. The solid formed (DTPA) was removed by filtration. The solvent was removed by rotary evaporation under reduced pressure. The DTPA bisamide (7) was purified from the residue by employing C-18 chromatography.

C) [N,N"-bis[N""-(2-hydroxyethyl)carbamoylmethyl-N'"-(2-hydroxyethyl)carbamoylmethyl]diethylenetriamine-N,N',N"-triacetate]]gadolinium(III)(8)



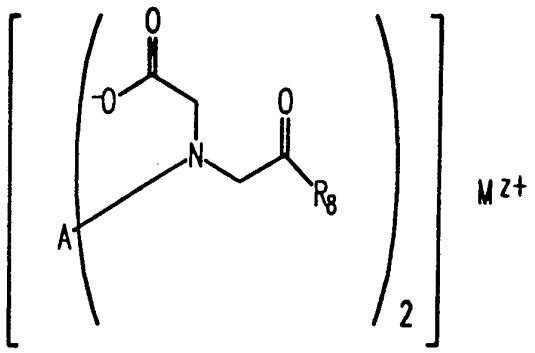
7 8

Gadolinium oxide (1.91 g, 5.27 m mol) was added to (7) (7.2 g, 10.6 m mol) in 50 ml of water. The mixture was stirred at 69°-71°C overnight. The solution was filtered and water was removed by rotary evaporation. The crude product (8) (9.2 g, 103.4%) was a white powder.

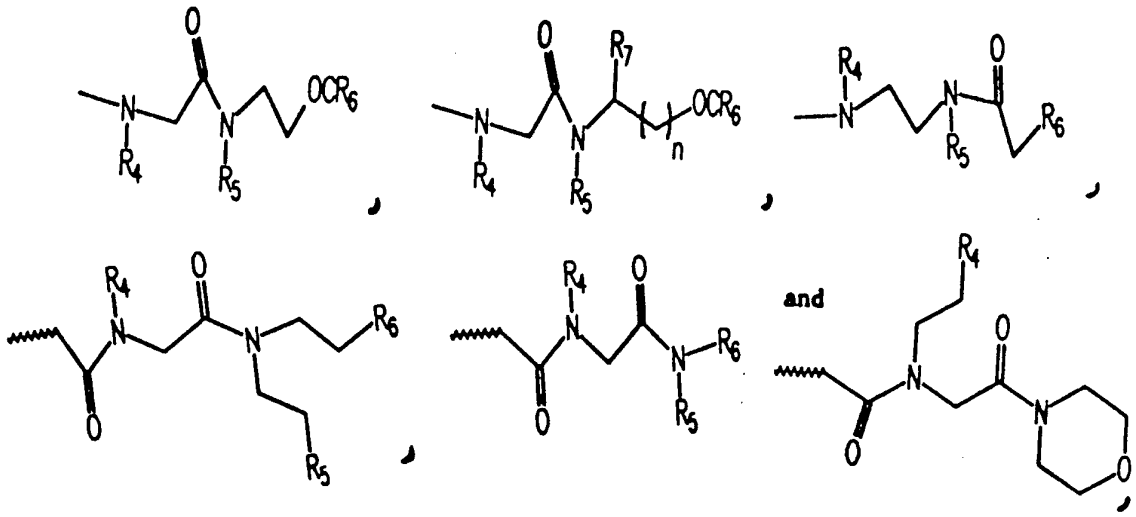
As various changes could be made in the above compounds and methods without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

What is claimed is:

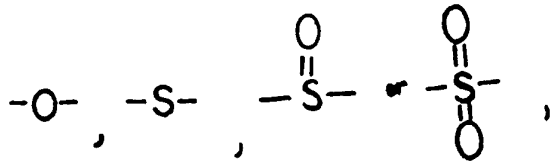
1. A complex comprising the following formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON$  O and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are

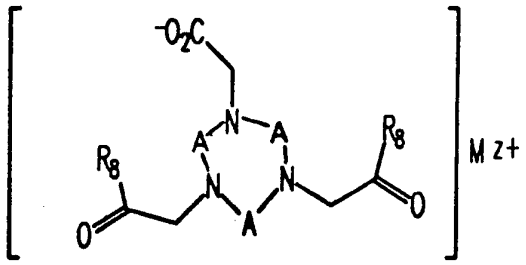


and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10; and M^{z+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope.

2. The complex of claim 1 wherein M^{z+} is chromium (III), manganese (II), manganese (III), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III).

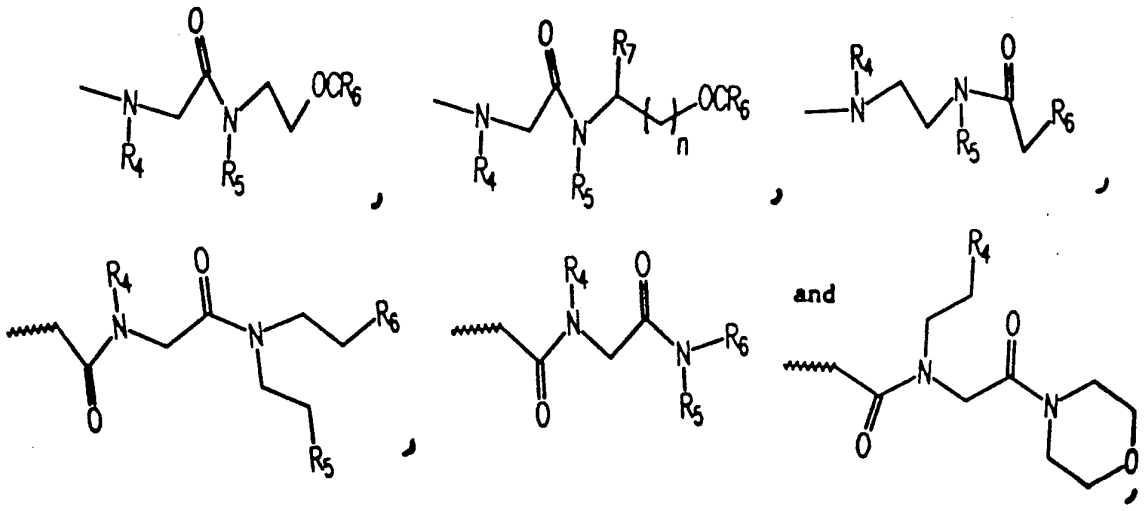
3. The complex of claim 1 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

4. A complex comprising the following formula:

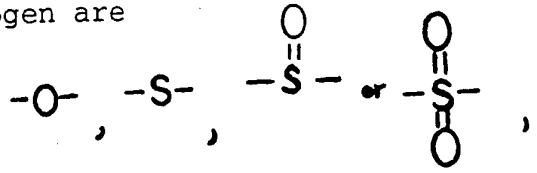


wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON\bigcirc O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a

substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are

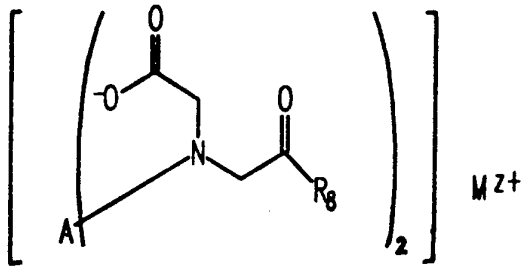


and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10; and M^{z+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope.

5. The complex of claim 4 wherein M^{z+} is chromium (III), manganese (II), manganese (III), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III).

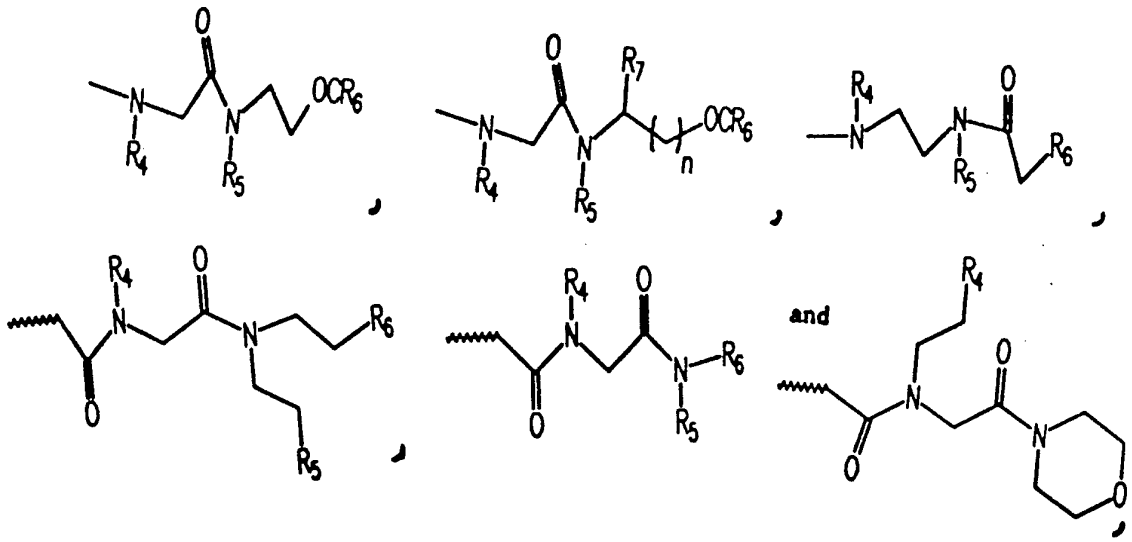
6. The complex of claim 4 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxye compounds such as amino sugar, carbohydrates and polysines.

7. A diagnostic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises an MRI-effective amount of a complex of a paramagnetic ion comprising the following formula:



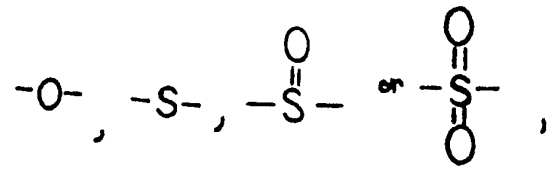
wherein A is selected from the group consisting of

$-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON$  and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono-

or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{z+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope; and a pharmaceutically acceptable carrier.

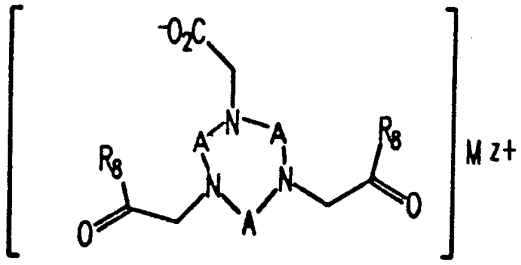
8. The diagnostic composition of claim 7 wherein M^{z+} is chromium (III), manganese (II), manganese (III), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III).

9. The diagnostic composition of claim 7 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

10. The diagnostic composition of claim 7 which further contains a pharmaceutically acceptable buffer.

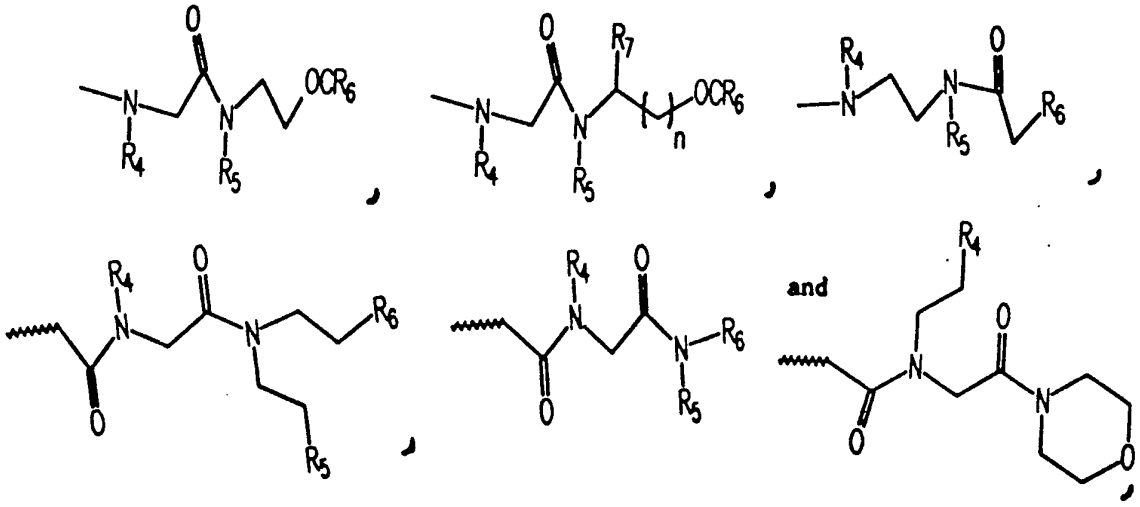
11. The diagnostic composition of claim 7 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

12. A diagnostic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises an MRI-effective amount of a complex of a paramagnetic ion comprising the following formula:

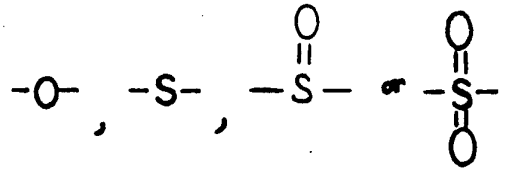


wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON\langle\rangle O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5,

6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{2+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope; and a pharmaceutically acceptable carrier.

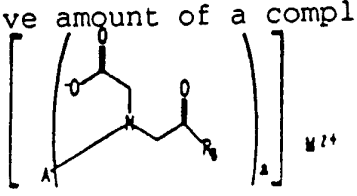
13. The diagnostic composition of claim 12 wherein M^{2+} is chromium (III), manganese (II), manganese (III), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III).

14. The diagnostic composition of claim 12 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

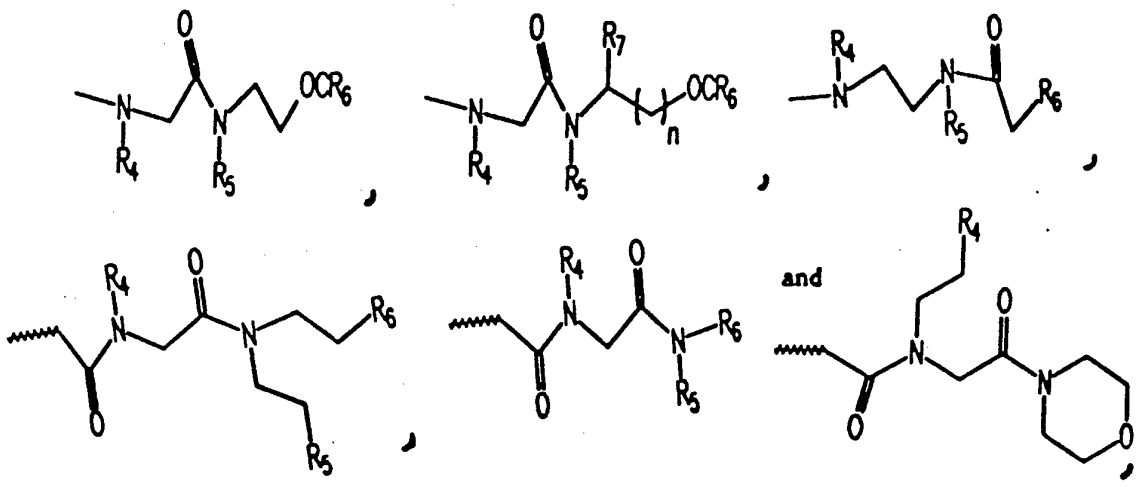
15. The diagnostic composition of claim 12 which further contains a pharmaceutically acceptable buffer.

16. The diagnostic composition of claim 12 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

17. A method of performing a diagnostic procedure, which comprises administering to a warm-blooded animal an effective amount of a complex of the formula:

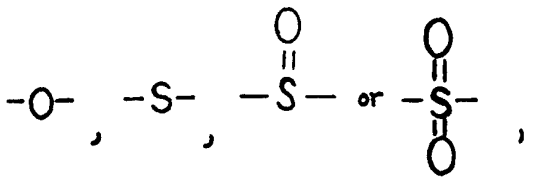


wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON\bigcirc O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same

or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



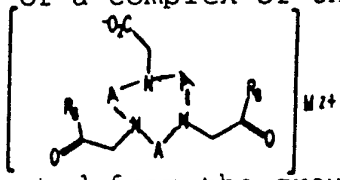
and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{2+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope; and a pharmaceutically acceptable carrier and then exposing the animal to an imaging procedure, thereby imaging at least a portion of the body of the warm-blooded animal.

18. The method of claim 17 wherein M^{2+} is chromium (III), manganese (II), manganese (III), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III).

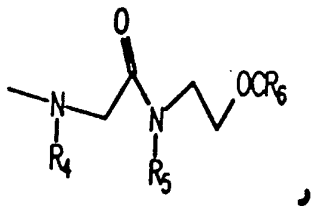
19. The method of claim 17 wherein said complex is attached to a biomolecule or polymeric compound

selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

20. A method of performing a diagnostic procedure, which comprises administering to a warm-blooded animal an effective amount of a complex of the formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON$  O and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including: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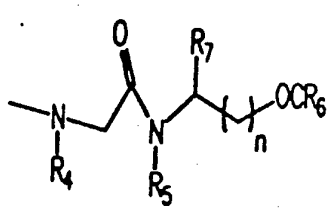
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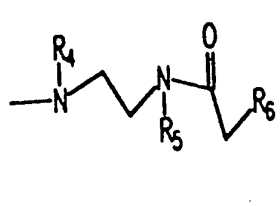
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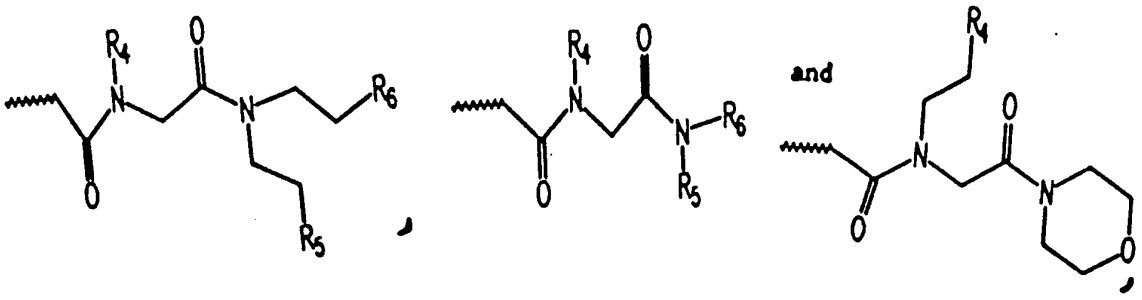
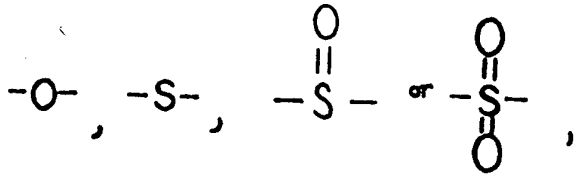


wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are

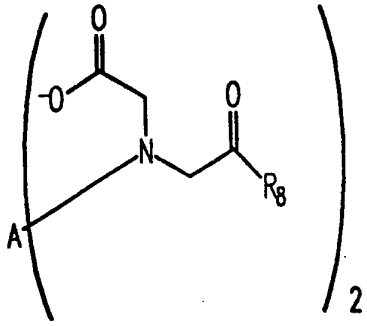


and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{2+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope; and a pharmaceutically acceptable carrier and then exposing the animal to an imaging procedure, thereby imaging at least a portion of the body of the warm-blooded animal.

21. The method of claim 20 wherein M^{2+} is chromium (III), manganese (II), manganese (III), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III).

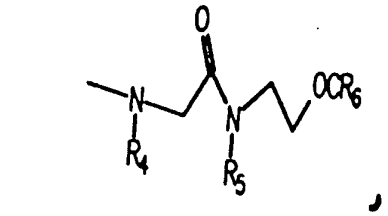
22. The method of claim 20 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugar, carbohydrates or polysines.

23. A complexing agent comprising the following formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON\bigcirc O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a

substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including: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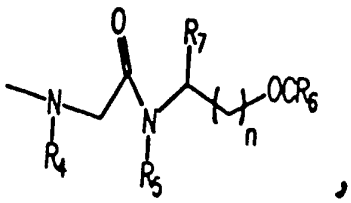
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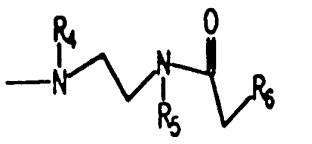
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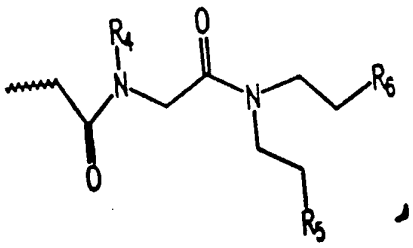
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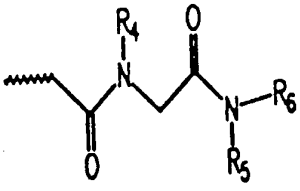
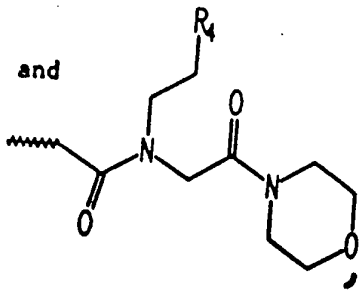

and

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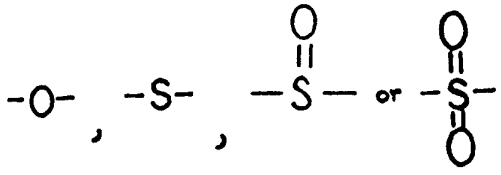
wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are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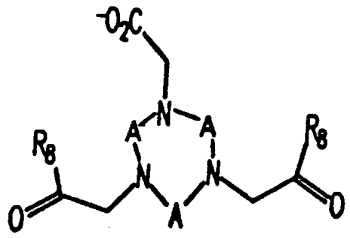
and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10; and M^{2+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope.

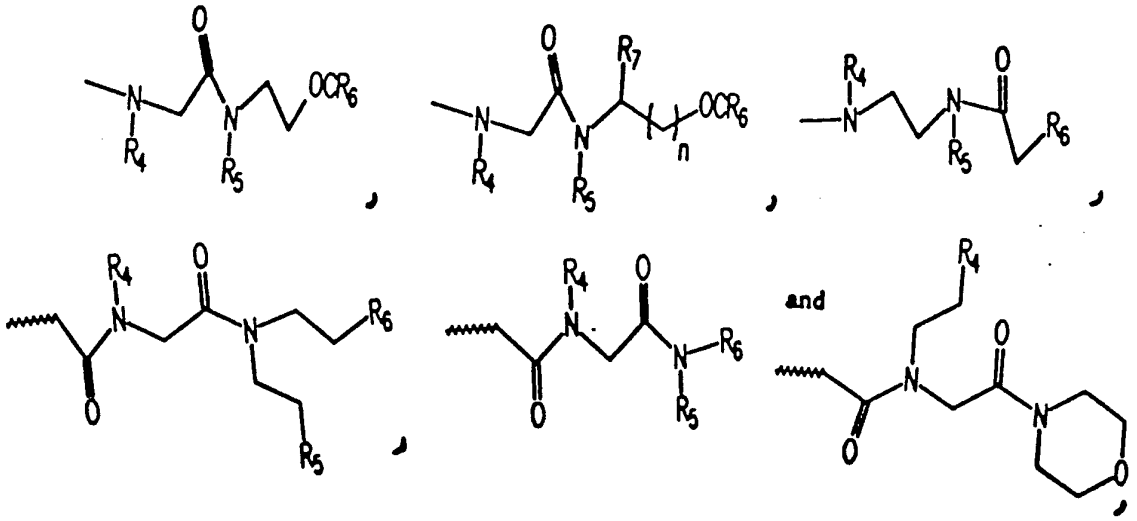
24. The complexing agent of claim 23 wherein said agent is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

25. A complexing agent comprising the following formula:



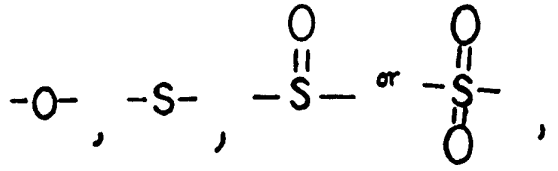
wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$,

$(CH_2)_nCONR_4(CH_2)_nCH_2CON$⬡$O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the

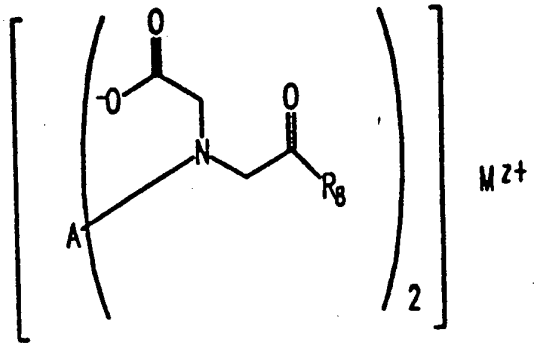
nitrogen are



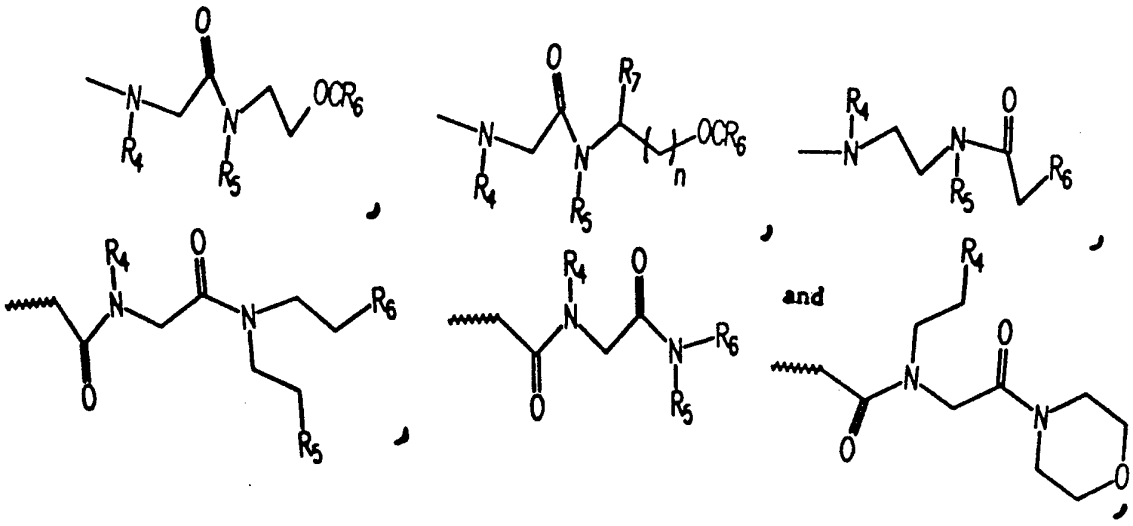
and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10; and M^{z+} is a paramagnetic metal ion, a heavy metal ion or a radioactive isotope.

26. The complexing agent of claim 25 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

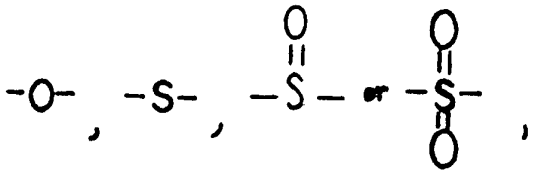
27. A diagnostic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises an imaging-effective amount of a complex of a heavy metal ion comprising the following formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON$  O and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{z+} is a heavy metal ion; and a pharmaceutically acceptable carrier.

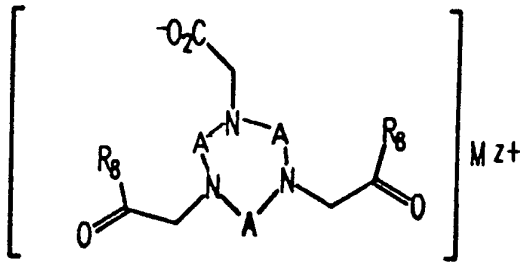
28. The diagnostic composition of claim 27 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

29. The diagnostic composition of claim 27 wherein M^{z+} is lead, bismuth or barium.

30. The diagnostic composition of claim 27 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

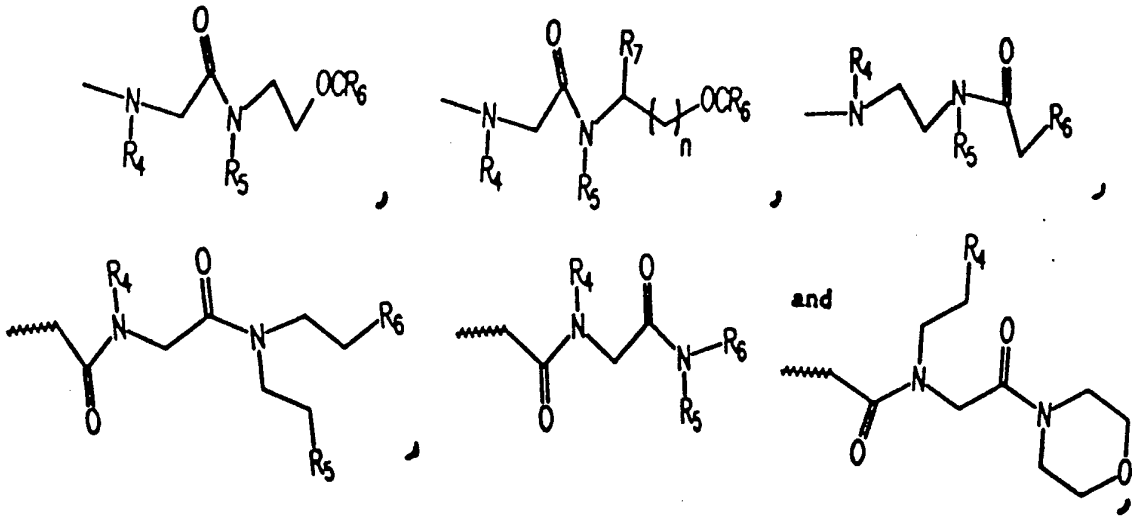
31. The diagnostic composition of claim 27 which further contains a pharmaceutically acceptable buffer.

32. A diagnostic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises an imaging-effective amount of a complex of a heavy metal ion comprising the following formula:

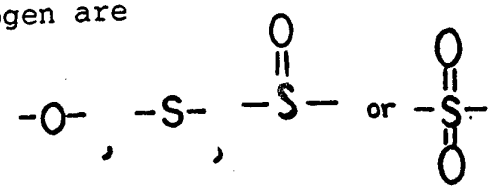


wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON\bigcirc O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a

substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{2+} is a heavy metal ion; and a pharmaceutically acceptable carrier.

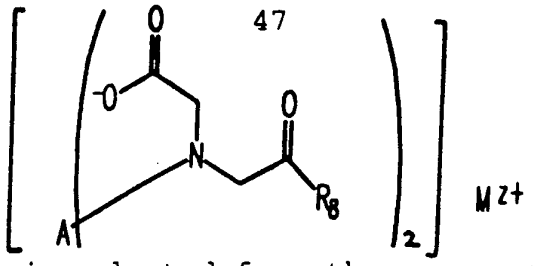
33. The diagnostic composition of claim 32 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

34. The diagnostic composition of claim 32 wherein M^{2+} is lead, bismuth or barium.

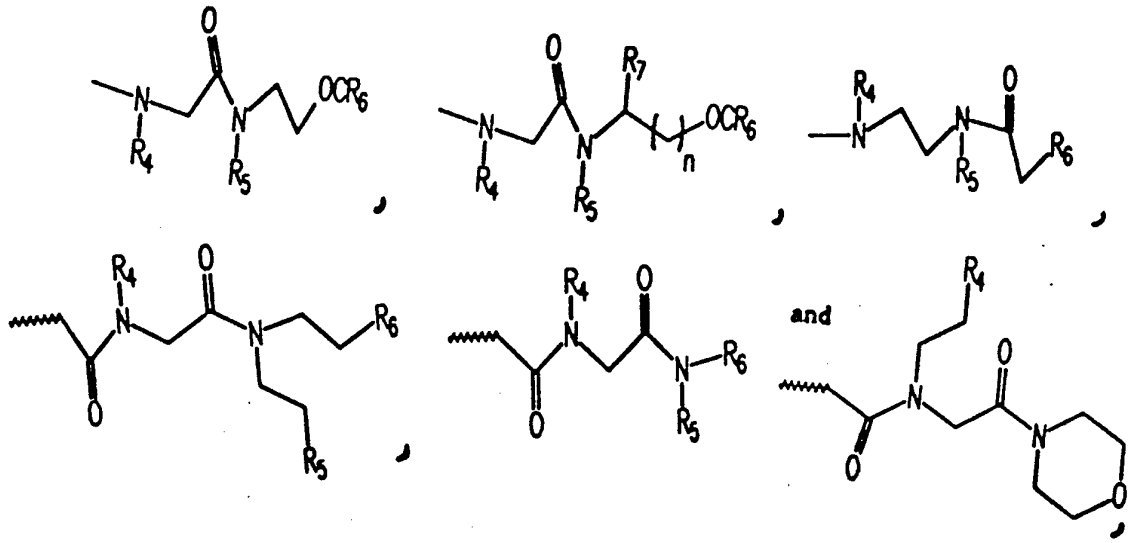
35. The diagnostic composition of claim 32 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

36. The diagnostic composition of claim 32 which further contains a pharmaceutically acceptable buffer.

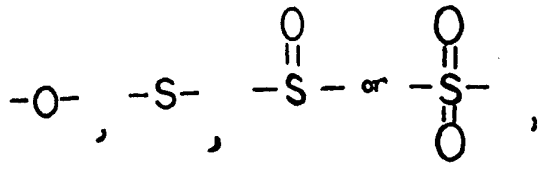
37. A diagnostic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises an imaging-effective amount of a radioactive isotope comprising the following formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON$  O and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{2+} is a radioactive isotope; and a pharmaceutically acceptable carrier.

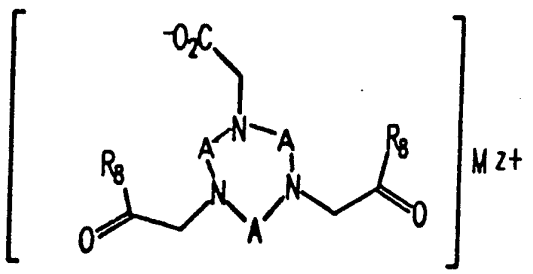
38. The diagnostic composition of claim 37 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

39. The diagnostic composition of claim 37 wherein M^{2+} is rhenium.

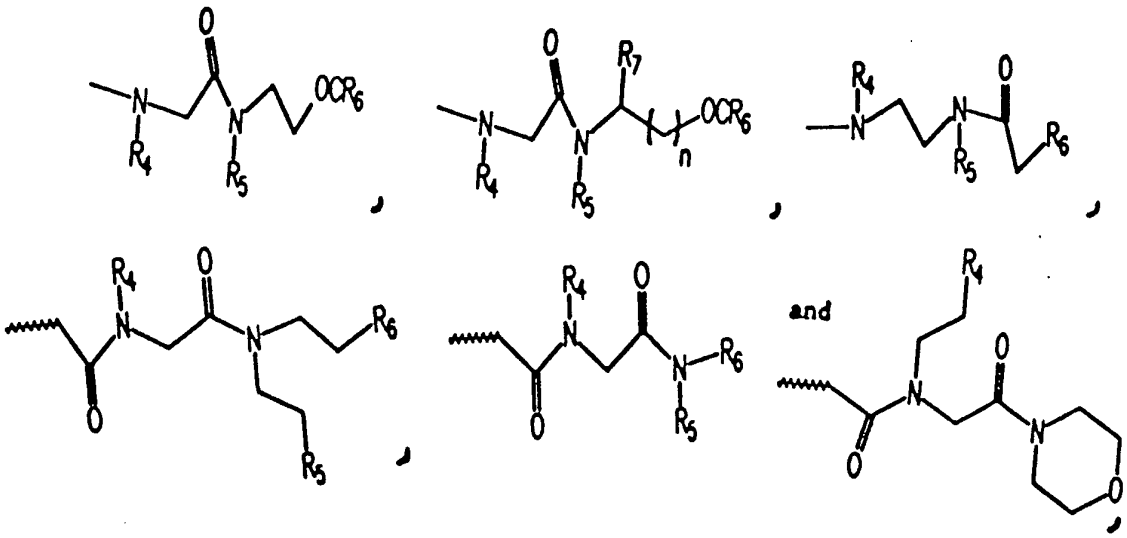
40. The diagnostic composition of claim 37 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

41. The diagnostic composition of claim 37 which further contains a pharmaceutically acceptable buffer.

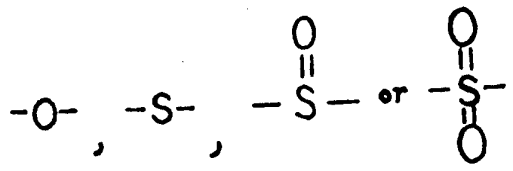
42. A diagnostic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises an imaging-effective amount of a radioactive isotope comprising the following formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON\bigcirc O$ and $-(CH_2)_nCONR_1(CH_2)_nCONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10}

aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 7 and M^{z+} is a radioactive isotope; and a pharmaceutically acceptable carrier.

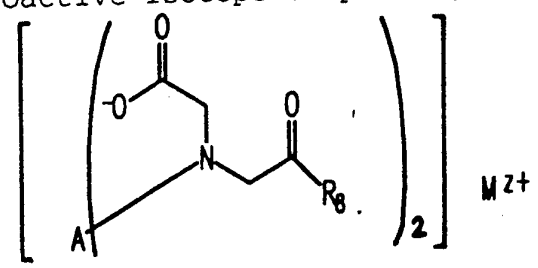
43. The diagnostic composition of claim 42 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

44. The diagnostic composition of claim 42 wherein M^{z+} is rhenium.

45. The diagnostic composition of claim 42 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

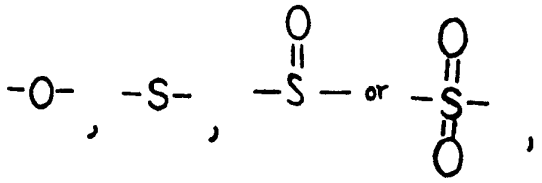
46. The diagnostic composition of claim 42 which further contains a pharmaceutically acceptable buffer.

47. A therapeutic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises a therapeutically-effective amount of a radioactive isotope comprising the following formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_nO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON$$O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:

wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl, carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{z+} is a radioactive isotope; and a pharmaceutically acceptable carrier.

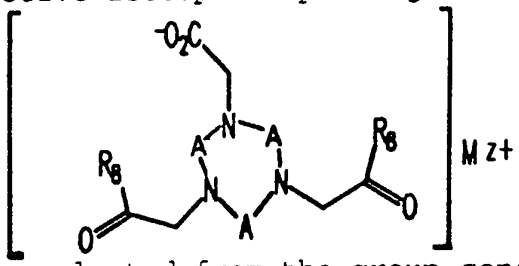
48. The therapeutic composition of claim 47 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

49. The therapeutic composition of claim 47 wherein M^{z+} is rhenium.

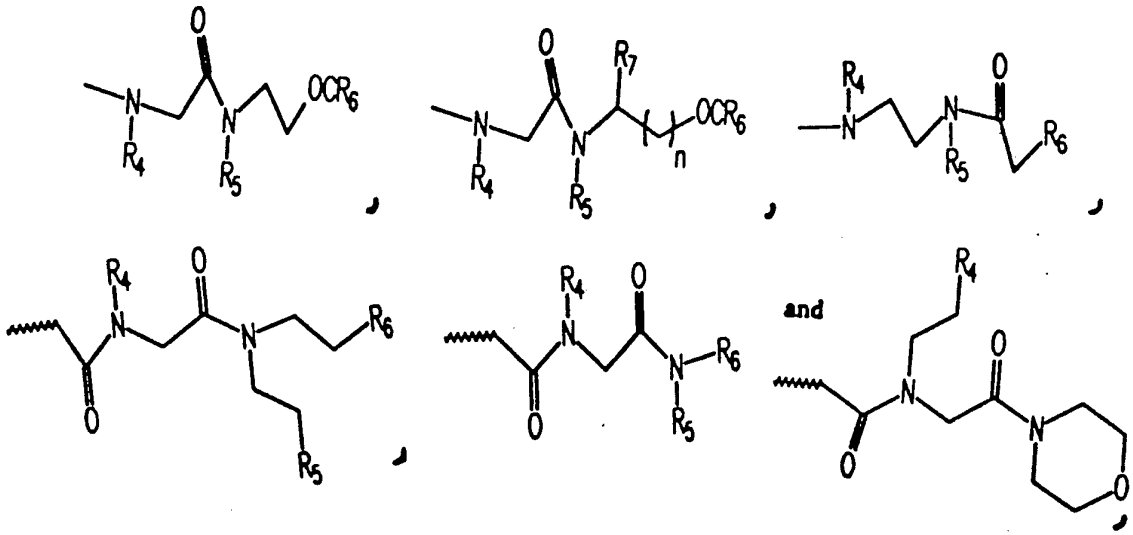
50. The therapeutic composition of claim 47 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

51. The therapeutic composition of claim 47 which further contains a pharmaceutically acceptable buffer.

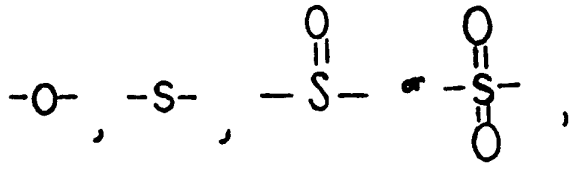
52. A therapeutic composition suitable for enteral or parenteral administration to a warm-blooded animal, which comprises a therapeutically-effective amount of a radioactive isotope comprising the following formula:



wherein A is selected from the group consisting of $-CHR_2CHOHCHR_3-$, $-CHR_2CHR_3[(NCHR_1COR_8)CHR_2CHR_3]_n-$, $-CHR_2CHR_3OCH_2CH_2-$ and $-CH_2CHR_2OCHR_3CH_2-$; R_8 is selected from the group consisting of $-O^-$, $-NR_4OR_5$, $-NR_4O(CH_2)_nR_6$, $-NR_4CH_2CONR_6CH_2CH_2OCH_2R_5$, $-NR_4(CH_2)_nNR_5$ $-COCH_2R_6$, $-(CH_2)_n-N_4CH_2CONR_6(CH_2)_rO(CH_2)_nOR_5$, $(CH_2)_nCONR_4(CH_2)_nCH_2CON\langle\rangle O$ and $-(CH_2)_nCONR_1(CH_2)_n$ $CONR_2R_3$; the R_1, R_2 and R_3 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkylalkoxy, C_{1-8} alkoxyalkyl, and C_{5-8} aryl, or wherein R_2 and R_3 as defined above together with the intervening carbon form a substituted or unsubstituted hydrocarbon ring of 5, 6 or 7 members, including:



wherein, the R_4, R_5, R_6 and R_7 groups may be the same or different selected from the group consisting of hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly- hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl and C_{1-12} acylaminoalkyl; the R_5 and R_6 groups together with the adjacent nitrogen can form a heterocyclic ring of five, six or seven members wherein 0 to 2 members of the ring other than the nitrogen are



and which members may be unsubstituted or substituted by hydrogen, C_{1-8} alkyl, C_{5-10} aryl, C_{5-10} aminoaryl, hydroxy, C_{1-8} alkoxy, C_{1-8} mono- or poly-hydroxyalkyl, C_{1-8} alkoxyalkyl, C_{1-8} aminoalkyl,

carbamoyl and C_{1-12} acylaminoalkyl; n is an integer between 0 and 10 and M^{2+} is a radioactive isotope; and a pharmaceutically acceptable carrier.

53. The therapeutic composition of claim 52 wherein said complex is attached to a biomolecule or polymeric compound selected from the group consisting of hormones, proteins, lipids, albumins, and polyhydroxyl compounds such as amino sugars, carbohydrates or polysines.

54. The therapeutic composition of claim 52 wherein M^{2+} is rhenium.

55. The therapeutic composition of claim 52 wherein the complex is dissolved or suspended in a sterile aqueous pharmaceutically acceptable carrier at a concentration of from about .05 to 1.0 M.

56. The therapeutic composition of claim 52 which further contains a pharmaceutically acceptable buffer.

INTERNATIONAL SEARCH REPORT

Inte .tional application No.
PCT/US93/09868

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A, 5,137,711 (WEBER et al.) 11 August 1992. See column 3, line 44 bridging column 4, line 48; Examples I-X, column 2, lines 32-44, and column 7, lines 10-20.	1,2,7-10,17 ,18,23,27-31,37-41,47-51
X	US, A, 5,094,950 (KONDO et al.) 10 March 1992. See column 3, lines 1-12; column 8, lines 44-55; column 9, lines 45-55.	23
X	US, A, 5,087,440 (CACHERIS et al.) 11 February 1992. See column 2, line 44 bridging column 3, line 35.	1,2,7-10,17,18,23
X	US, A, 4,957,939 (GRIES et al.) 18 September 1990. See column 1, line 40 bridging column 2, line 55; column 3 lines 57-66; column 4, lines 1-68;	1-56
X	EP, A, 255 471 (SCHERING) 03 February 1988. See Example 19, page 55 which discloses a paramagnetic complex of N-(Morpholinocarbonylmethyl)-1,4,7,10 tetrazacyclododecane- N', N'', N''' -triaceticacid.	4-6,12-16-20-22,25,26, 28-36,42-46,52-56
X,P	EP, A, 512,661 (SCHERING) 11 November 1992. See pages 7 through 9.	25,26,4-6,12-16,20-22, 28-36,42-46,52-56
X	DE, A, 3633245 (SCHERING) 31 March 1988. See page 6 and Examples 1 through 4.	23,24,1-3,7-11,17-19,27-31,37-41,47-51
X	EP, A, 450,742 (SCHERING) 09 October 1991. See pages, 4 through 6.	23,24,1-3,7-11,17-19,27-31,37-41,47-51
X	WO, A 90/01024 (MALLINCKRODT) 08 February 1990. See pages 7 and 8.	1,2,7-10,17,18,23,27-31,37-41,47-51
Y	US, A, 4,980,148 (DEAN) 25 December 1990. See the abstract.	1,2,7-10,17,18,23,27-31,37-41,47-51
X	US, A, 5,011,925 (RAJAGOPALAN et al.) 30 April 1991. See column 3, line 42 bridging column 4, line 25; column 6 line 34 bridging column 7, line 39; and column 9, lines 48-59	1-56

INTERNATIONAL SEARCH REPORT

Inte ational application No.
PCT/US93/09868

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 49/00, 02, 04
US CL : 424/1.65,4,9;534/10,15,16;540/465,474;
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)

U.S. : 424/1.65,4,9;534/10,15,16;540/465,474;

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

IPC A61K 49/00, 02 US: 128/653.4

Electronic data base consulted during the international search (name of data base and, where practicable, 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 ---- Y	US, A, 5,138,040 (MOORE et al.) 11 August 1992. See the entire document.	1-3,7-11,17-19,23,24,27-31,37-41, 47-51 ---------- 1-56
X	US, A, 4,687,658 (QUAY) 18 August 1987, See column 2, lines 9-35.	1,2,7-10,17, 18,23
A	US, A, 4,687,659 (QUAY) 18 August 1987. See column 2, lines 10-35.	1 , 2 , 7 - 1 0 , 17,18,23
X	US, A, 5,141,740 (RAJAGOPALAN et al) 25 August 1992. See column 3, line 38 bridging column 4, line 57;column 5, lines 18-36; and column 7, lines 23-34	1-56

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 31 JANUARY 1994	Date of mailing of the international search report MAR 21 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOHN M. COVERT Telephone No. (703) 305-0444

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

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US93/09868

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

This international 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:

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:
Telephone Practice

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.