

Physiologically tolerable metal complex salts for use  
in diagnosis

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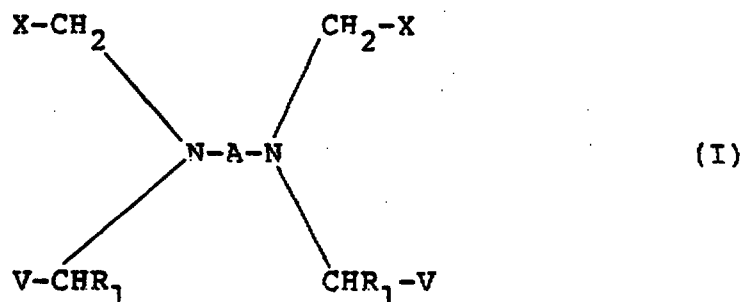
The invention relates to physiologically tolerable metal complex salts and the use thereof in diagnosis.

5       Complex compounds and their salts have been used for a long time in medicine, for example as auxiliaries for the administration of sparingly soluble ions (for example iron) and as antidotes (calcium or zinc complexes being preferred in this case) for detoxication in the  
10 case of inadvertent incorporation of heavy metals or their radioactive isotopes.

The present application and related application No. 85.29901 (publication No. 2 169 598) are divisional applications from patent application No. 84.01486  
15 (publication No. 2 137 612).

We have now found that certain physiologically tolerable complex salts containing one or more central elements having the atomic numbers of from 21 to 29, 42, 44 and from 57 to 83 can be used for the manufacture of  
20 preparations that are surprisingly outstandingly suitable for use in NMR, ultra-sound, and X-ray diagnostics.

The present invention provides a physiologically tolerable, non-radioactive complex salt for use in a method of diagnosis of the human or animal body by NMR  
25 diagnosis, X-ray diagnosis or ultra-sound diagnosis having the general formula I



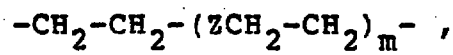
in which

X represents the radicals  $\text{-COOY}$ ,  $\text{-PO}_3\text{HY}$  or  $\text{-CONHOY}$  wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid,

and in which either

10 a)  $\text{R}_1$  represents in each case a hydrogen atom or methyl group,

A represents the group  $\text{-CHR}_2\text{-CHR}_3\text{-}$  or



in which

15  $\text{R}_2$  and  $\text{R}_3$  together represent a trimethylene group or a tetramethylene group,

or each represents a phenyl radical  
or benzyl radical,

m represents the integer 1, 2 or 3,

and

5            z represents an oxygen atom or a  
sulphur atom,

and

each V has the same meaning as X,

with the proviso that at least two of the substituents

10 Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
83, and with the further proviso that when R<sub>2</sub> and  
R<sub>3</sub> represent a tetramethylene group at least one Y is  
neither an iron equivalent nor a hydrogen atom,

15 or

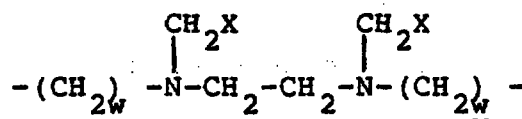
b) R<sub>1</sub> represents in each case a hydrogen atom,

A represents the group -CH<sub>2</sub>-CH<sub>2</sub>-

and

both V's together represent the group

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in which

X has the meanings given above

and

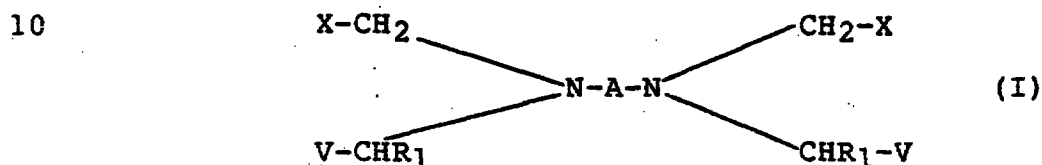
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w represents the integer 1, 2 or 3,

with the proviso that at least two of the substituents

Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83.

The present invention further provides a diagnostic preparation for use in a method of diagnosis of the human or animal body by NMR diagnosis, X-ray diagnosis or ultra-sound diagnosis, comprising (i) a physiologically tolerable, non-radioactive complex salt of the general formula I



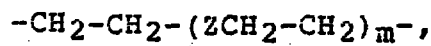
in which

X represents the radicals  $-\text{COOY}$ ,  $-\text{PO}_3\text{HY}$  or  $-\text{CONHOY}$  wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid,

and in which either

a)  $\text{R}_1$  represents in each case a hydrogen atom or methyl group,

A represents the group  $-\text{CHR}_2\text{-CHR}_3-$  or



in which

$\text{R}_2$  and  $\text{R}_3$  together represent a trimethylene group or a tetramethylene group,

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or each represents a phenyl radical  
or benzyl radical,

m represents the integer 1, 2 or 3,

and

5            z represents an oxygen atom or a  
sulphur atom,

and

each V has the same meaning as X,

with the proviso that at least two of the substituents

10    Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
83, and with the further proviso that when R<sub>2</sub> and  
R<sub>3</sub> represent a tetramethylene group at least one Y is  
neither an iron equivalent nor a hydrogen atom,

15    or

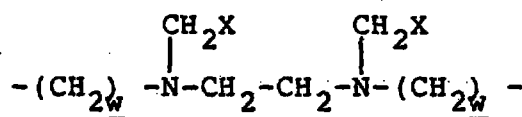
b)    R<sub>1</sub> represents in each case a hydrogen atom,

A represents the group -CH<sub>2</sub>-CH<sub>2</sub>-

and

both V's together represent the group

20



in which

X has the meanings given above

and

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w represents the integer 1, 2 or 3,

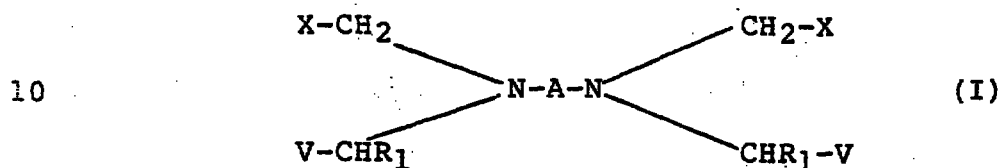
with the proviso that at least two of the substituents

Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83,

and

- 5 (ii) a physiologically tolerable carrier.

The present invention also provides a physiologically tolerable, non-radioactive complex salt of the general formula I



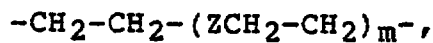
in which

X represents the radicals -COOY, -PO<sub>3</sub>HY or -CONHOY wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid,

and in which either

- 20 a) R<sub>1</sub> represents in each case a hydrogen atom or methyl group,

A represents the group -CHR<sub>2</sub>-CHR<sub>3</sub>- or



in which

- 25 R<sub>2</sub> and R<sub>3</sub> together represent a trimethylene group or a tetramethylene group, with the proviso that when R<sub>2</sub> and R<sub>3</sub> together represent a

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tetramethylene group, at least one Y  
represents a physiologically  
tolerable cation of an organic base  
or amino acid, or each represents a  
phenyl radical or benzyl radical,  
represents the integer 1, 2 or 3,

5

m

and

Z

represents an oxygen atom or a  
sulphur atom,

10 and

each V has the same meaning as X,

with the proviso that at least two of the substituents  
Y are metal equivalents selected from elements having  
atomic number of from 21 to 29, 42, 44 and from 57 to

15 83,

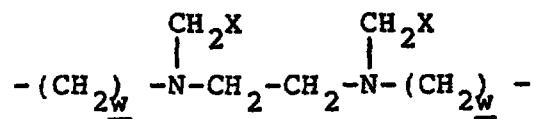
or

b) R<sub>1</sub> represents in each case a hydrogen atom,

A represents the group -CH<sub>2</sub>-CH<sub>2</sub>-

and

20 both V's together represent the group



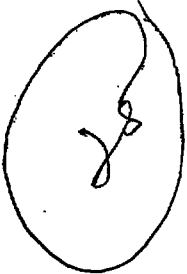
in which

X has the meanings given above

25

and

w represents the integer 1, 2 or 3,



with the proviso that at least two of the substituents Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83.

5           Moreover, the present invention further provides a diagnostic preparation comprising (i) a physiologically tolerable, non-radioactive complex salt of the general formula I, as defined in the preceding paragraph, and (ii) a physiologically tolerable carrier.

10           Thus, the physiologically tolerable complex salt of the general formula I may be regarded as containing

(a) a central element selected from elements having atomic numbers of from 21 to 29 inclusive, 42, 44 and from 57 to 83 inclusive, and (b) a radical of a physiologically tolerable complex-forming acid and, if  
5 desired, (c) a radical selected from radicals of inorganic and organic bases and amino acids.

The physiologically tolerable complex salts of the general formula I may contain more than one such central element (a) and more than one such radical (c).

10 For the intended use of the diagnostic agent according to the invention, the element or elements having an atomic number mentioned above, which forms the central element or elements of the physiologically tolerable complex salt, must not, of course, be  
15 radioactive.

In the case where a preparation of the invention is to be used in NMR diagnostics (see European Patent Application 71 564), the central element of the complex salt must be paramagnetic. Such elements are



especially the divalent and trivalent elements having an atomic number of from 21 to 29, 42, 44 and from 58 to 70. Suitable elements are, for example, chromium(III), manganese(II), iron(III), iron(II), cobalt(II), nickel(II), copper(II), praseodymium(III), neodymium(III), samarium(III) and ytterbium(III). Especially preferred, owing to their strong magnetic moment, are gadolinium(III), terbium(III), dysprosium(III), holmium(III) and erbium(III).

10 If the preparation of the invention is to be used in X-ray diagnostics, the central element must be one having a relatively high atomic number in order to obtain sufficient absorption of the X-rays. It has been found that diagnostic preparations that  
15 comprise a physiologically tolerable complex salt containing a central element or elements having an atomic number of from 57 to 83 are suitable for this purpose; such elements are, for example, lanthanum(III), the above-mentioned elements of the  
20 lanthanide series, gold(III), lead(II) or, especially, bismuth(III).

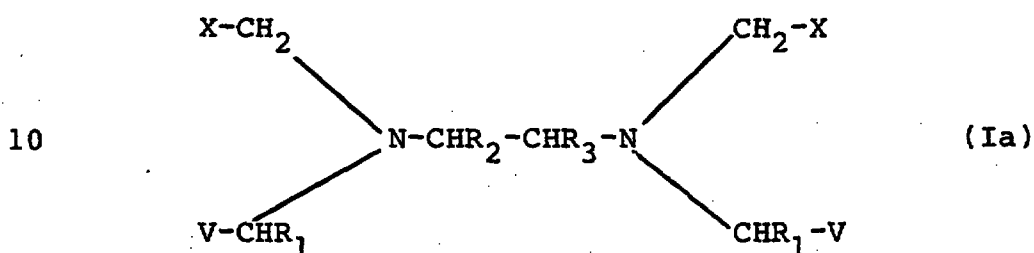
The preparations of the invention that are to be used in NMR diagnostics and those that are to be used in X-ray diagnostics are also suitable for use in  
25 ultra-sound diagnostics.

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The complex-forming acids from which the physiologically tolerable complex salts of the general formula I may be derived are, especially, those containing carboxymethylene groups. The complex-forming acids carry optionally two central elements, and especially one central element.

Suitable complex salts of the general formula I for use in accordance with the present invention above are, for example, those of the general formula Ia



in which  $R_1$  represents in each case a hydrogen atom or methyl group, each V has the same meaning as X and X,  $R_2$  and  $R_3$  have the meanings given above.

The following complex-forming acids, inter alia, are suitable for the manufacture of the complex salts of the general formula Ia:-

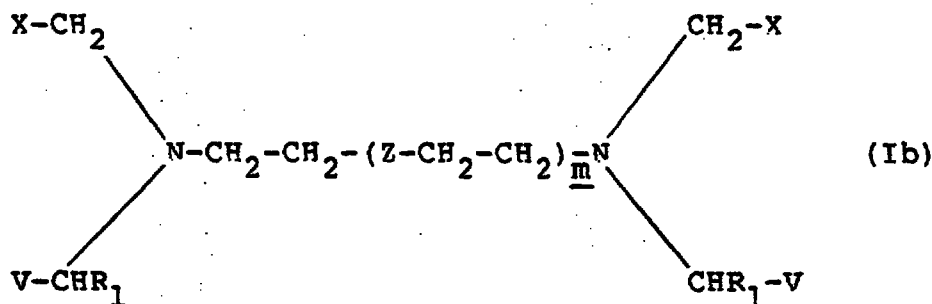
trans-1,2-cyclohexylenediaminetetraacetic acid and 1,2-diphenylethylenediaminetetraacetic acid.

Other suitable complex salts of the general formula I are, for example, those of the general

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formula Ib

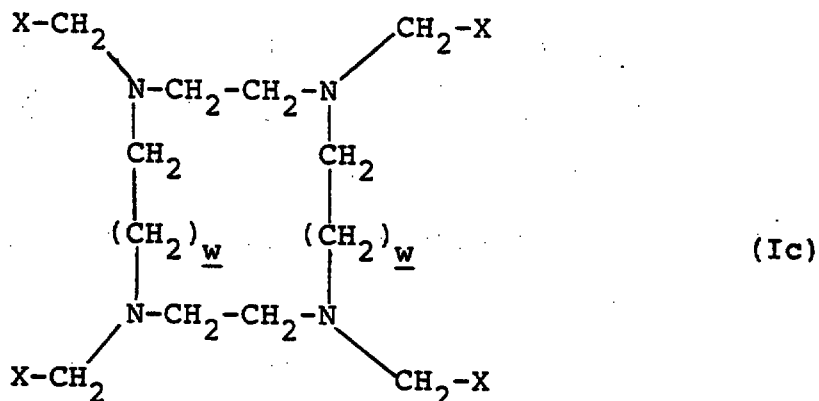


in which  $R_1$  represents in each case a hydrogen atom or methyl group, each V has the same meaning as X and X, Z and  $\underline{m}$  have the meanings given above. Of the complex salts of the general formula Ib those in which  $\underline{m}$  represents 1 or 2 are preferred.

The following complex-forming acids, inter alia, are suitable for the manufacture of the complex salts of the general formula Ib:

1,10-diaza-4,7-dioxadecane-1,1,10,10-tetraacetic acid and 1,10-diaza-4,7-dithiadecane-1,1,10,10-tetraacetic acid.

Suitable complex salts of the general formula I are also those of the general formula Ic



in which X and w have the meanings given above.

The following complex-forming acids, inter alia, are suitable for the manufacture of the complex salts of the general formula Ic:

1,4,8,11-tetraazacyclotetradecanetetraacetic acid and, especially, 1,4,7,10-tetraazacyclododecanetetraacetic acid.

If not all of the acid hydrogen atoms of the complex-forming acid are substituted by the central element or elements, it is advantageous, for the purpose of increasing the solubility of the complex salt, to substitute the remaining hydrogen atoms by physiologically tolerable cations of inorganic and/or organic bases or amino acids. Suitable inorganic cations are for example, lithium, potassium or, especially, sodium. Suitable cations of organic bases are, inter alia, those of primary, secondary or tertiary amines, such as, for example, ethanolamine,

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diethanolamine, morpholine, glucamine, N,N-dimethylglucamine or, especially, N-methylglucamine. Suitable cations of amino acids are, for example, those of lysine, arginine or ornithine.

- 5           The complex-forming acids required for the formation of the complex salts of the general formula I are known or can be manufactured in a manner known per se.

- 10           The manufacture of the complex salts of the general formula I can likewise be carried out in a manner known per se by dissolving or suspending the metal oxide or metal salt (for example the nitrate, chloride or sulphate) of the element having an atomic number of from 21 to 29, 42, 44 or from 57 to 83 in  
15   water and/or a lower alcohol (such as methanol, ethanol or isopropanol) and adding a solution or suspension of the equivalent amount of the complex-forming acid in water and/or a lower alcohol, and stirring, if  
20   necessary while warming or heating to boiling point, until the reaction is complete. If the complex salt formed is insoluble in the solvent used, it is isolated by filtration. If it is soluble, it can be isolated by concentrating the solution to dryness by evaporation, for example by means of spray-drying.

- 25           If acid groups are still present in the resulting complex salt, it is often advantageous to convert the acid complex salt into a neutral complex salt or salts

by means of inorganic and/or organic bases or amino acids that form physiologically tolerable cations and to isolate the neutral salt. In many cases, this is indeed unavoidable since the dissociation of the  
5 complex salt is so suppressed by the shift in the pH value to neutral that only in that manner can uniform products be at all isolated or at least purified.

The manufacture is advantageously carried out with the aid of organic bases or basic amino acids.  
10 It can, however, also be advantageous if the neutralisation is carried out by means of inorganic bases (hydroxides, carbonates or bicarbonates) of sodium, potassium or lithium.

For the manufacture of the neutral salts there  
15 may, for example, be added to the acid complex salts in aqueous solution or suspension as much of the desired base as is necessary to obtain the neutral point. The resulting solution can subsequently be concentrated to dryness in vacuo. It is frequently of  
20 advantage to precipitate the resulting neutral salts by adding water-miscible solvents, such as, for example, lower alcohols (methanol, ethanol, isopropanol, etc.), lower ketones (acetone, etc.), and polar ethers (tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.), and  
25 thus obtain crystallisates that are easily isolated and readily purified. It has been found especially advantageous to add the desired base to the reaction

mixture during the complex formation and thereby dispense with one process step.

If the acid complex salts contain several free acid groups, it is often advantageous to produce neutral mixed salts that contain both inorganic and organic physiologically tolerable cations as ions of opposite charge. This can be effected, for example, by reacting the complex-forming acid in aqueous suspension or solution with the oxide or salt of the element supplying the central element and with half the amount of organic base required for neutralisation, isolating the complex salt formed, if desired purifying it, and then adding to it the amount of inorganic base required for complete neutralisation. The order in which the bases are added can also be reversed.

The manufacture of the diagnostic preparations according to the invention is likewise effected in a manner known per se by suspending or dissolving the complex salts in an aqueous medium, for example water or physiological salt solution, optionally with the addition of the additives customary in galenical pharmacy, and subsequently sterilising the solution or suspension. Suitable additives are, for example, physiologically tolerable buffers (such as, for example, tromethamine hydrochloride), small additions of complex formers (such as, for example, diethylenetriaminepentaacetic acid) or, if necessary,

electrolytes (such as, for example, sodium chloride).

In principle, it is also possible to manufacture the diagnostic preparations of the invention even without isolating the complex salts. In each case, particular care must be taken to effect the chelate formation in such a manner that the salts and salt solutions according to the invention are virtually free of non-complexed toxically acting metal ions. This can be ensured, for example, with the aid of colour indicators, such as xylenol orange, by test titrations during the manufacturing process. The invention also therefore provides processes for the manufacture of the complex salts and of the aforesaid preparations containing them. As a final safeguard, there is always purification of the isolated complex salt.

If suspensions of the complex salts in water or physiological salt solution are desired for oral administration or other purposes, a sparingly soluble complex salt is mixed with one or more auxiliaries customary in galenical pharmacy and/or surfactants and/or aromatic substances for taste correction.

The diagnostic preparations of the invention contain preferably from 1  $\mu\text{mol}$  to 1 mol per litre of the complex salt and are, as a rule, administered in doses of from 0.001 to 5 mmol/kg. They are intended for oral, and especially parenteral, administration. If desired, they may be in a dosage form suitable for

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administration orally, neurally or intravasally. When the preparations are in a form suitable for injection, they may be contained in ampoules.

The diagnostic preparations of the invention meet

5 the many requirements for suitability as contrast agents for nuclear spin tomography. For example, after oral or parenteral administration, they are

outstandingly suitable for improving the information that can be provided by the image obtained with the aid

10 of nuclear spin tomography, as a result of increasing the signal intensity. They also exhibit the high activity necessary to keep to a minimum the amount of foreign substances introduced into the body and the good tolerability necessary to maintain the non-

15 invasive character of the examination (the compounds mentioned in J. Comput. Tomography 5,6: 543-46 (1981), in Radiology 144, 343 (1982) and in Brevet Special de Medicament No. 484 M (1960) are, for example, too

20 toxic). The ready water-solubility of the complex salts used in the preparations of the invention enables the preparation of highly concentrated solutions, so that the volume introduced into the circulation can be kept within reasonable limits and the dilution by body fluid can be compensated, that is to say the NMR

25 diagnostic preparations must be 100 to 1000 times more water-soluble than is necessary for NMR spectroscopy. Furthermore, the diagnostic preparations of the

invention are not only highly stable in vitro but also exhibit a surprisingly high stability in vivo, so that the per se toxic ions that are not covalently bonded in the complexes are released or exchanged only  
5 extremely slowly over the 24 hours in which, as pharmacological studies have shown, the novel contrast agents are completely eliminated.

The diagnostic preparations of the invention, particularly those in which the physiologically  
10 tolerable complex salt contains an element having a relatively high atomic number that is from 57 to 83, for example 71 to 83, are also outstandingly suitable as X-ray contrast agents; it should be especially emphasised that, with these, none of the symptoms of  
15 anaphylaxy-type reactions known in the case of iodine-containing contrast agents can be detected in biochemical-pharmacological tests. They are especially valuable by virtue of their advantageous absorption properties in regions of relatively high tube voltages  
20 for digital subtraction techniques.

Further, the diagnostic preparations of the invention are also suitable as ultra-sound diagnostics owing to their property of favourably influencing the ultra-sound speed.

25 In contrast to conventional X-ray diagnostics with shadow-producing X-ray contrast agents, in NMR diagnostics with paramagnetic contrast agents there is

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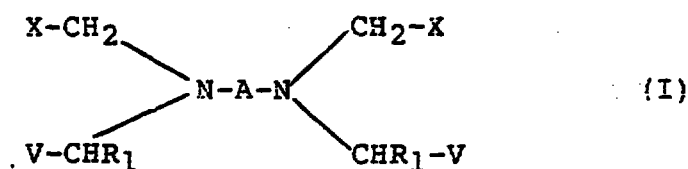
no linear relationship between the signal intensification and the concentration used. As control studies have shown, increasing the dose administered does not necessarily result in the signal being intensified, and, in the case of a high dose of paramagnetic contrast agent, the signal can even be extinguished. It was, for that reason, surprising that some pathological processes become visible only after the administration of doses higher than those specified in EP 71 564 (which may be from 0.001 mmol/kg to 5 mmol/kg) of a preparation of the invention containing a strongly paramagnetic contrast agent. Thus, for example, a defective blood-brain barrier in the region of a cranial abscess can be demonstrated only after giving 0.05 to 2.5 mmol/kg, preferably 0.1 - 0.5 mmol/kg, of paramagnetic complex salts such as, for example, manganese 1,2-cyclohexylenediaminetetraacetic acid in the form of its readily water-soluble salts. For a dose of more than 0.1 mmol/kg, solutions of higher concentrations of up to 1 mol/l, preferably from 0.25 to 0.75 mol/l, are required since only in this way is the volume reduced and the ease of handling the injection solution ensured.

Especially low doses (under 1 mg/kg) and therewith solutions of lower concentrations (1  $\mu$ mol/l to 5 mmol/l) than are specified in EP 71 564 are required for organ-specific NMR diagnostics, for

example for detecting tumours and coronary infarcts.

The physiologically tolerable, non-radioactive complex salts of the general formula I, as defined above, may contain a metal selected, for example, from elements having atomic numbers of from 71 to 83. It may be advantageous for at least one of the substituents Y to be a physiologically tolerable cation of an organic base or amino acid.

The present invention further provides the use of a physiologically tolerable, non-radioactive complex salt of the general formula I,



in which

X represents the radicals  $\text{-COOY}$ ,  $\text{PO}_3\text{HY}$  or  $\text{-CONHOY}$  wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid, and in which either

a)  $\text{R}_1$  represents in each case a hydrogen atom or methyl group,

A represents the group  $\text{-CHR}_2\text{-CHR}_3\text{-}$  or  $\text{-CH}_2\text{-CH}_2\text{-(ZCH}_2\text{-CH}_2\text{)}_{\underline{m}}\text{-}$ , in which

R<sub>2</sub> and R<sub>3</sub> together represent a trimethylene group  
or a tetramethylene group,  
or each represents a phenyl radical or  
benzyl radical,

5     m     represents the integer 1, 2 or 3,

and

z     represents an oxygen atom or a sulphur  
atom,

and

10   each V has the same meaning as X,  
with the proviso that at least two of the substituents  
Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
83,

15   or

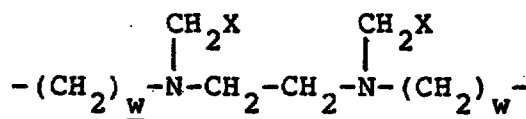
b) R<sub>1</sub> represents in each case a hydrogen atom,

A represents the group -CH<sub>2</sub>-CH<sub>2</sub>

and

both V's together represent the group

20



in which

X has the meanings given above

and

25   w represents the integer 1, 2 or 3,

with the proviso that at least two of the substituents

Y are metal equivalents selected from the elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, for the manufacture of a preparation for a method of diagnosis of the human or animal body by NMR,

5 X-ray or ultra-sound diagnosis.

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The following Examples illustrate the invention:-

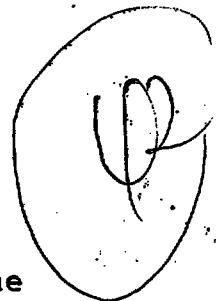
Example 1

The salts listed below are obtained in a manner analogous to the manufacture described below of the N-methylglucamine salt of the iron(III) complex of diethylenetriaminepentaacetic acid, using the appropriate acid in place of the diethylenetriaminepentaacetic acid and using sodium hydroxide solution in place of the N-methylglucamine when manufacturing the sodium salts:-

the sodium salt of the iron(III) complex of trans-1,2-cyclohexylenediaminetetraacetic acid,  $C_{14}H_{18}FeN_2O_8 \cdot Na$ ;

the sodium salt of the iron(III) complex of 1,10-diaza-4,7-dioxadecane-1,1,10,10-tetraacetic acid,  $C_{14}H_{20}FeN_2O_{10} \cdot Na$ , and

the N-methylglucamine salt of the iron(III) complex of trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid,  $C_{21}H_{36}FeN_3O_{13}$ .



Manufacture of the N-methylglucamine salt of the iron(III) complex of diethylenetriaminepentaacetic acid,  $C_{21}H_{37}FeN_4O_{15}$

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35.4 g (= 90 mmol) of diethylenetriaminepenta-  
5 acetic acid are suspended in 100 ml of water, and  
24.3 g (= 90 mmol) of iron(III) chloride hexahydrate  
( $FeCl_3 \cdot 6 H_2O$ ), dissolved in 100 ml of water, are  
added thereto. The initially dark brown suspension is  
heated to 95°C. After approximately 1 hour, the  
10 colour changes to a light yellow. 270 ml of 1N sodium  
hydroxide solution are added to neutralise the  
hydrochloric acid formed and the whole is heated for a  
further 3 hours at 95°C. The resulting light yellow  
precipitate is suction-filtered, washed free of  
15 chloride with water and dried at 60°C in vacuo.  
17.85 g (45 % of the theoretical yield) of a light  
yellow powder is obtained the melting point of which  
is >300°C.

17.85 g (= 40 mmol) of the iron(III) complex  
20 salt obtained are suspended in 200 ml of water, and  
7.8 g (= 40 mmol) of solid N-methylglucamine are added  
in portions. The whole is heated for approximately 3  
hours at 50°C and an almost clear, red-brown solution  
is obtained which is filtered and then concentrated to  
25 dryness in vacuo. The residue is dried at 50°C in

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vacuo. 24.3 g (95 % of the theoretical yield) of a red-brown powder of melting point 131-133°C are obtained.

Example 2

- 5 Manufacture of the N-methylglucamine salt of the gadolinium(III) complex of trans-1,2-cyclohexylene-diamine-N,N,N',N'-tetraacetic acid,  $C_{21}H_{36}GdN_3O_{13}$
- 

20.78 g (= 60 mmol) of trans-1,2-cyclohexylene-diamine-N,N,N',N'-tetraacetic acid are suspended in  
10 150 ml of water. After the addition of 11.7 g  
(= 60 mmol) of N-methylglucamine, an almost clear solution is obtained to which 10.88 g (= 30 mmol) of gadolinium oxide ( $Gd_2O_3$ ) are added. The suspension again obtained is heated for 6 hours at 95°C. The  
15 small amount of undissolved material is filtered off and the filtrate is concentrated to dryness in vacuo. The residue is dried in vacuo at 60°C and pulverised. 38.6 g (92 % of the theoretical yield) of a white powder of melting point 258-261°C are obtained.

20 Analysis:

|              |         |        |        |          |
|--------------|---------|--------|--------|----------|
| (calculated) | C 36.25 | H 5.22 | N 6.04 | Gd 22.60 |
| (found)      | C 36.40 | H 5.50 | N 5.98 | Gd 22.52 |



In analogous manner, by using sodium hydroxide solution in place of N-methylglucamine, the sodium salt of the gadolinium(III) complex of trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid,

5  $C_{14}H_{18}GdN_2O_8 \cdot Na$ , is obtained.

### Example 3

Preparation of the disodium salt of the manganese(II) complex of trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid,  $C_{14}H_{16}MnN_2O_8 \cdot 2 Na$

---

10 Under nitrogen, 34.6 g (= 100 mmol) of trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid are suspended in 100 ml of water, and 11.5 g (= 100 mmol) of manganese(II) carbonate,  $MnCO_3$ , are added. The whole is heated to 95°C and 200 ml of 1N  
15 sodium hydroxide solution are added dropwise thereto. The clear solution is concentrated in vacuo and the residue is dried in vacuo at 60°C. 40.8 g (92 % of the theoretical yield) of a pink-coloured powder are obtained.

### 20 Analysis:

|              |         |        |        |          |
|--------------|---------|--------|--------|----------|
| (calculated) | C 37.94 | H 4.09 | N 6.32 | Mn 12.40 |
| (found)      | C 37.78 | H 4.12 | N 6.20 | Mn 12.31 |

In analogous manner, there are obtained:

from copper(II) carbonate the disodium salt of the copper(II) complex of trans-1,2-cyclohexylenediamine-tetraacetic acid,  $C_{14}H_{18}CuN_2O_8 \cdot 2 Na$ ;

- 5 from cobalt(II) carbonate the disodium salt of the cobalt(II) complex of trans-1,2-cyclohexylenediamine-tetraacetic acid,  $C_{14}H_{18}CoN_2O_8 \cdot 2 Na$ ;

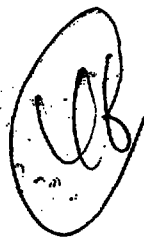
- from nickel(II) carbonate the disodium salt of the nickel(II) complex of trans-1,2-cyclohexylenediamine-  
10 tetraacetic acid,  $C_{14}H_{18}NiN_2O_8 \cdot 2 Na$ .

By using N-methylglucamine in place of sodium hydroxide solution there is obtained:

- the di-N-methylglucamine salt of the manganese(II) complex of trans-1,2-cyclohexylenediaminetetraacetic  
15 acid,  $C_{28}H_{54}MnN_4O_{18}$ .

#### Example 4

Each of the two salts listed below are obtained in a manner analogous to the preparation described below of the N-methylglucamine salt of the



gadolinium(III) complex of ethylenediamine-N,N,N',N'-  
tetracetic acid, using 1,10-diaza-4,7-dioxadecane-  
1,1,10,10-tetraacetic acid in place of ethylenediamine-  
N,N,N',N'-tetracetic acid when preparing the  
5 first-listed salt and, similarly, using 1,2-diphenyl-  
ethylenediaminetetraacetic acid when preparing the  
second-listed salt:-

the N-methylglucamine salt of the gadolinium(III)  
complex of 1,10-diaza-4,7-dioxadecane-1,1,10,10-tetra-  
10 acetic acid,  $C_{21}H_{38}GdN_3O_{15}$ , and  
the N-methylglucamine salt of the gadolinium(III)  
complex of 1,2-diphenylethylenediaminetetraacetic acid,  
 $C_{29}H_{38}N_3O_{13}Gd$ .

Preparation of the N-methylglucamine salt of the  
15 gadolinium(III) complex of ethylenediamine-N,N,N',N'-  
tetracetic acid,  $C_{17}H_{30}GdN_3O_{13}$

---

29.2 g ( = 100 mmol) of ethylenediamine-N,N,N',N'-  
tetracetic acid are suspended in 100 ml of water and  
heated to 95°C with 18.1 g ( = 50 mmol) of  
20 gadolinium(III) oxide,  $Gd_2O_3$ . During the heating-up  
process, 19.5 g ( = 100 mmol) of N-methylglucamine are  
added in portions. After approximately 3 hours, a

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clear solution is obtained which is filtered and concentrated to dryness in vacuo. The residue is dried at 60°C in vacuo. 61.3 g (95 % of the theoretical yield) of a white powder having an

5 indeterminate melting point are obtained.

Analysis:

|              |         |        |        |          |
|--------------|---------|--------|--------|----------|
| (calculated) | C 31.82 | H 4.71 | N 6.55 | Gd 24.51 |
| (found)      | C 31.65 | H 4.59 | N 6.52 | Gd 24.56 |

Example 5

10 Preparation of the sodium salt of the gadolinium(III) complex of 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid,  $C_{16}H_{24}GdN_4O_8 \cdot Na$

---

4.0 g (= 10 mmol) of 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid are suspended in

15 20 ml of water, and 10 ml of 1N sodium hydroxide solution are added. 1.8 g (= 5 mmol) of gadolinium(III) oxide,  $Gd_2O_3$ , are added and the suspension is heated for 2 hours at 50°C. The clear solution is filtered and concentrated in vacuo. The

20 residue is dried and pulverised. 5.5 g (95 % of the theoretical yield) of a white powder are obtained.

Analysis:

|              |         |        |        |          |
|--------------|---------|--------|--------|----------|
| (calculated) | C 33.10 | H 4.17 | N 9.65 | Gd 27.08 |
| (found)      | C 33.01 | H 4.20 | N 9.57 | Gd 27.16 |

In analogous manner there are obtained:

- 5 the N-methylglucamine salt of the gadolinium(III) complex of 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid,  $C_{23}H_{42}GdN_5O_{13}$ ;

- the sodium salt of the gadolinium(III) complex of 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid,  $C_{18}H_{28}GdN_4O_8 \cdot Na$ .
- 10

Example 6

Preparation of a solution of the N-methylglucamine salt of the gadolinium(III) complex of 1,4,7,10-tetraazacyclododecanetetraacetic acid

---

- 15 370.9 g ( = 500 mmol) of the complex salt described in Example 5 are made into a paste in 500 ml of water p.i. (pro injectione) and dissolved by making up the volume to 1000 ml with water p.i.. The solution is introduced into ampoules and heat-sterilised.

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Example 7

Preparation of a solution of the di-N-methylglucamine salt of the manganese(II) complex of trans-1,2-cyclohexylenediaminetetraacetic acid

---

- 5            395.9 g ( = 500 mmol) of the complex salt described in Example 3 are suspended in 500 ml of water p.i. 1.3 g of ascorbic acid are added and the suspension is dissolved by making up the volume to 1000 ml with water p.i. The solution is sterile-filtered and
- 10 placed in ampoules.

Example 8

Preparation of a solution of the N-methylglucamine salt of the gadolinium(III) complex of trans-1,2-cyclohexylenediaminetetraacetic acid

---

- 15            555.8 g ( = 0.8 mol) of the salt described in Example 2 are dissolved in water p.i. to a volume of 1000 ml. After filtration over a pyrogen filter, the solution is placed in ampoules and heat-sterilised.

Example 9

Preparation of a solution of the N-methylglucamine salt of the ruthenium(III) complex of 1,10-diaza-4,7-dithiadecane-1,1,10,10-tetraacetic acid

---

5            15.6 g ( = 0.03 mmol) of the ruthenium(III) complex of 1,10-diaza-4,7-dithiadecane-1,1,10,10-tetraacetic acid are suspended in 50 ml of water p.i. and dissolved at pH 7.5 by adding 5.9 g ( = 0.03 mol) of N-methylglucamine. The solution is made up to 1000 ml  
10 with water p.i., placed in ampoules and heat-sterilised.

Example 10

Preparation of a solution of the sodium salt of the gadolinium(III) complex of trans-1,2-cyclohexylene-diaminetetraacetic acid  
15

---

558.6 g ( = 1 mol) of the sodium salt of the complex salt listed in Example 2 are dissolved in water p.i. and made up to 1000 ml. The solution is placed in bottles and heat-sterilised.

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Example 11

Preparation of a solution of the N-methylglucamine salt of the gadolinium(III) complex of 1,2-diphenylethylenediaminetetraacetic acid

---

- 5            396.9 g ( = 500 mmol) of the N-methylglucamine salt of the complex salt containing gadolinium and the 1,2-diphenylethylenediaminetetraacetic acid radical listed in Example 4 are made into a paste in 600 ml of water p.i. and dissolved by making up the volume to  
10 1000 ml. The solution is placed in ampoules and heat-sterilised.

Example 12

- Preparation of a solution of the disodium salt of the manganese(II) complex of trans-1,2-cyclohexylenediaminetetraacetic acid  
15
- 

- Under nitrogen, 44.3 g ( = 100 mmol) of the complex salt described in Example 3 are made into a paste in 60 ml of water p.i. and dissolved by making up the volume to 100 ml with water p.i.. The solution  
20 is placed in ampoules and heat-sterilised.

Example 13

Preparation of a solution of the sodium salt of the gadolinium(III) complex of 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid

---

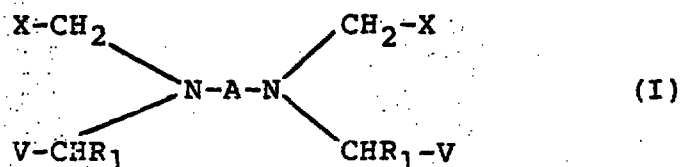
- 5            552.6 g ( = 1 mol) of the complex salt containing gadolinium and the 1,4,8,11-tetraazacyclotetradecane-tetraacetic acid radical listed in Example 5 are dissolved in water p.i. and made up to 1000 ml. The solution is placed in bottles and heat-sterilised.



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Claims

1. A physiologically tolerable, non-radioactive complex salt for use in a method of diagnosis of the human or animal body by NMR diagnosis, X-ray diagnosis or ultra-sound diagnosis having the general formula I



in which

- 10 X represents the radicals  $\text{-COOY}$ ,  $\text{PO}_3\text{HY}$  or  $\text{-CONHOY}$  wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid,
- and in which either
- a)  $\text{R}_1$  represents in each case a hydrogen atom or methyl group,

- A represents the group  $\text{-CHR}_2\text{-CHR}_3\text{-}$  or
- 20  $\text{-CH}_2\text{-CH}_2\text{-(ZCH}_2\text{-CH}_2\text{)}_{\underline{m}}\text{-}$ ,

in which

- $\text{R}_2$  and  $\text{R}_3$  together represent a trimethylene group or a tetramethylene group,



or each represents a phenyl radical or benzyl radical,

m represents the integer 1, 2 or 3,

and

5 z represents an oxygen atom or a sulphur atom,

and

each V has the same meaning as X,

with the proviso that at least two of the substituents

10 Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, and with the further proviso that when R<sub>2</sub> and R<sub>3</sub> represent a tetramethylene group at least one Y is neither an iron equivalent nor a hydrogen atom,

15 or

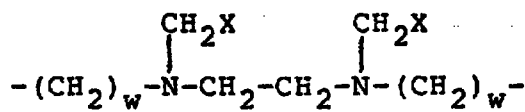
b) R<sub>1</sub> represents in each case a hydrogen atom,

A represents the group -CH<sub>2</sub>-CH<sub>2</sub>-

and

both V's together represent the group

20



in which

X has the meanings given above

and

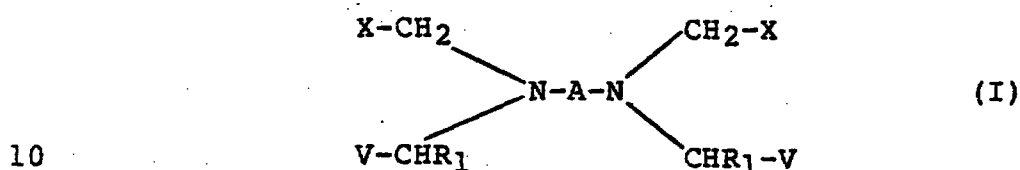
25 w represents the integer 1, 2 or 3,

with the proviso that at least two of the substituents



Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83.

2. A physiologically tolerable, non-radioactive complex salt for use in a method of diagnosis of the human or animal body by NMR diagnosis, X-ray diagnosis or ultra-sound diagnosis having the general formula I



in which

X represents the radicals -COOY, -PO<sub>3</sub>HY or -CONHOY, wherein at least one of the substituents Y is a physiologically tolerable cation of an organic base or amino acid, and any remaining Y is a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic base,

20 and in which either

a) R<sub>1</sub> represents in each case a hydrogen atom or methyl group,

A represents the group -CHR<sub>2</sub>-CHR<sub>3</sub>-or -CH<sub>2</sub>-CH<sub>2</sub>-(ZCH<sub>2</sub>-CH<sub>2</sub>)<sub>m</sub><sup>-</sup>,

25 in which



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R<sub>2</sub> and R<sub>3</sub> together represent a trimethylene group or a tetramethylene group, or each represents a phenyl radical or benzyl radical,

5     m     represents the integer 1, 2 or 3,  
and

      Z     represents an oxygen atom or a sulphur atom,

and

10    each V has the same meaning as X,  
with the proviso that at least two of the substituents Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83,

15    or

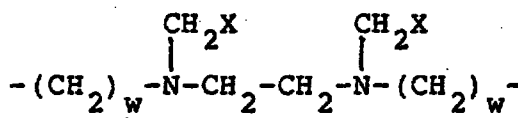
b) R<sub>1</sub> represents in each case a hydrogen atom,

A represents the group -CH<sub>2</sub>-CH<sub>2</sub>-

and

both V's together represent the group

20



in which

X has the meanings given above

and

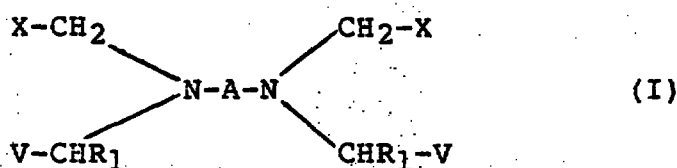
25     w represents the integer 1, 2 or 3,

with the proviso that at least two of the substituents Y are metal equivalents selected from elements having



atomic numbers of from 21 to 29, 42, 44 and from 57 to 83.

3. The use of a physiologically tolerable, complex salt for the manufacture of a preparation for a method of diagnosis of the human or animal body by NMR diagnosis, X-ray diagnosis or ultra-sound diagnosis, the said complex salt having the general formula I



in which

X represents the radicals  $\text{-COOY}$ ,  $\text{PO}_3\text{HY}$  or  $\text{-CONHOY}$  wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid, and in which either

a)  $\text{R}_1$  represents in each case a hydrogen atom or methyl group,

A represents the group  $\text{-CHR}_2\text{-CHR}_3\text{-}$  or  $\text{-CH}_2\text{-CH}_2\text{-(ZCH}_2\text{-CH}_2\text{)}_{\text{m}}\text{-}$ ,

in which

$\text{R}_2$  and  $\text{R}_3$  together represent a trimethylene group or a tetramethylene group, or each represents a phenyl radical or



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benzyl radical,

m represents the integer 1, 2 or 3,

and

z represents an oxygen atom or a sulphur  
atom,

and

each V has the same meaning as X,

with the proviso that at least two of the substituents  
Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
83,

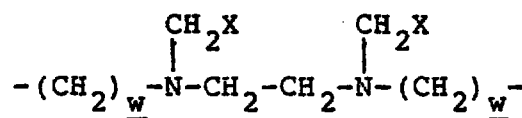
or

b)  $R_1$  represents in each case a hydrogen atom,

A represents the group  $-CH_2-CH_2-$

and

both V's together represent the group



in which

X has the meanings given above

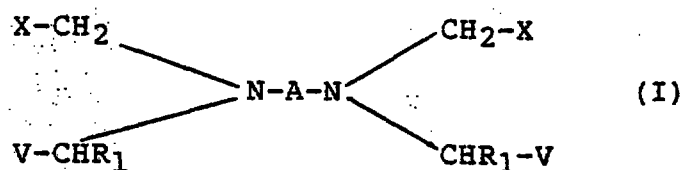
and

w represents the integer 1, 2 or 3,

with the proviso that at least two of the  
substituents Y are metal equivalents  
selected from elements having atomic  
numbers of from 21 to 29, 42, 44 and from  
57 to 83.



4. A diagnostic preparation for use in a method of diagnosis of the human or animal body by NMR diagnosis, X-ray diagnosis or ultra-sound diagnosis, comprising (i) a physiologically tolerable, non-radioactive complex salt of the general formula I



in which

- 10 X represents the radicals  $-\text{COOY}$ ,  $-\text{PO}_3\text{HY}$  or  $-\text{CONHOY}$  wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid, and in which either

a)  $\text{R}_1$  represents in each case a hydrogen atom or methyl group,

A represents the group  $-\text{CHR}_2\text{-CHR}_3-$  or

- 20  $-\text{CH}_2\text{-CH}_2\text{-(ZCH}_2\text{-CH}_2\text{)}_{\underline{\text{m}}}-$ ,

in which

$\text{R}_2$  and  $\text{R}_3$  together represent a trimethylene group or a tetramethylene group, or each represents a phenyl radical or benzyl radical,



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m represents the integer 1, 2 or 3,  
and  
Z represents an oxygen atom or a  
sulphur atom,

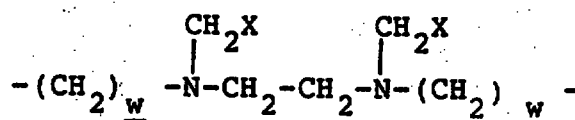
5 and  
each V has the same meaning as X,  
with the proviso that at least two of the substituents  
Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
10 83, and with the further proviso that when R<sub>2</sub> and  
R<sub>3</sub> represent a tetramethylene group at least one Y is  
neither an iron equivalent nor a hydrogen atom,  
or  
b) R<sub>1</sub> represents in each case a hydrogen atom,



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A represents the group <sup>674</sup>-CH<sub>2</sub>-CH<sub>2</sub>-

and

both V's together represent the group



5 in which

X has the meanings given above

and

w represents the integer 1, 2 or 3,

with the proviso that at least two of the substituents

10 Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
83,

and

(ii) a physiologically tolerable carrier.

15 . 5. A diagnostic preparation as claimed in claim 4,  
wherein the complex salt (i) is the disodium salt of  
the manganese (II) complex of trans-1,2-  
cyclohexylenediaminetetraacetic acid.

6. A diagnostic preparation as claimed in claim 4,  
20 substantially as described in any one of Examples 6 to  
13 herein.

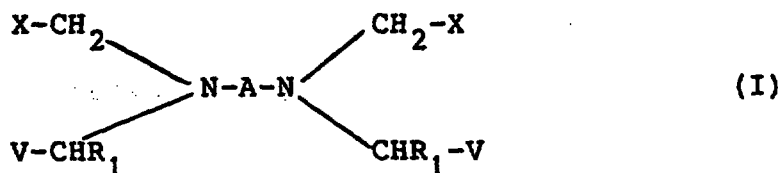


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7. A process for the manufacture of a diagnostic preparation as claimed in claim 4, conducted substantially as described in any one of Examples 6 to 13 herein.

- 5 8. A diagnostic preparation which comprises  
(i) a physiologically tolerable, non-radioactive complex salt of the general formula I



in which

- 10 X represents the radicals -COOY, -PO<sub>3</sub>HY or -CONHOY wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an  
15 inorganic or organic base or amino acid,  
and in which either  
a) R<sub>1</sub> represents in each case a hydrogen atom or methyl group,

A represents the group -CHR<sub>2</sub>-CHR<sub>3</sub>- or

- 20 -CH<sub>2</sub>-CH<sub>2</sub>-(ZCH<sub>2</sub>-CH<sub>2</sub>)m-,  
in which

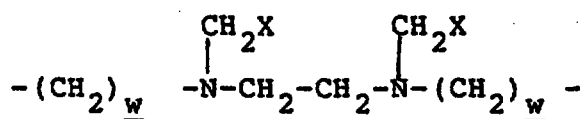
R<sub>2</sub> and R<sub>3</sub> together represent a trimethylene group



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5 or a tetramethylene group,  
with the proviso that when R<sub>2</sub> and R<sub>3</sub>  
together represent a tetramethylene  
group, at least one Y represents a  
physiologically tolerable cation of an  
organic base or amino acid,  
or each represents a phenyl radical or  
benzyl radical,  
m represents the integer 1, 2 or 3,  
10 and  
z represents an oxygen atom or a sulphur  
atom,  
and  
each V has the same meaning as X,  
15 with the proviso that at least two of the substituents  
Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
83,  
or  
20 b) R<sub>1</sub> represents in each case a hydrogen atom,  
A represents the group -CH<sub>2</sub>-CH<sub>2</sub>-  
and  
both V's together represent the group



25 in which



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X has the meanings given above  
and

w represents the integer 1, 2 or 3,

with the proviso that at least two of the substituents

5 Y are metal equivalents selected from elements having  
atomic numbers of from 21 to 29, 42, 44 and from 57 to  
83;

and

(ii) a physiologically tolerable carrier.

10 9. A diagnostic preparation as claimed in claim 4 or  
claim 8, wherein the carrier (ii) is an aqueous  
carrier.

10. A diagnostic preparation as claimed in claim 9,  
wherein the carrier (ii) is water or physiological salt  
15 solution, and the complex salt (i) is dissolved or  
suspended in it.

11. A diagnostic preparation as claimed in claim 9 or  
claim 10, wherein the complex salt (i) is present in a  
concentration of from 1  $\mu$ mol to 1 mol per litre.

20 12. A diagnostic preparation as claimed in any one of  
claim 4 and claims 8 to 11, wherein the complex salt  
(i) is derived from trans-1,2-cyclohexylene-  
diaminetetraacetic acid, 1,4,7,10-tetraazacyclododecane-  
tetraacetic acid or 1,4,8,11-tetraazacyclotetra-  
25 decanetetraacetic acid.



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13. A diagnostic preparation as claimed in any one of claim 4 and claims 8 to 12, wherein the complex salt (i) is the di-N-methylglucamine salt of the manganese (II) complex of trans-1,2-cyclohexylenediaminetetra-  
5 acetic acid.

14. A diagnostic preparation as claimed in any one of claim 4 and claims 8 to 12, wherein the complex salt (i) is the N-methylglucamine salt of the gadolinium (III) complex of 1,4,7,10-tetraazacyclododecanetetra-  
10 acetic acid.

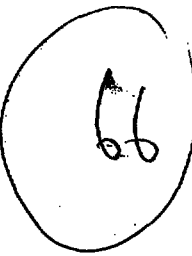
15. A diagnostic preparation as claimed in any one of claim 4 and claims 8 to 12, wherein the complex salt (i) is the sodium salt of the gadolinium (III) complex of 1,4,7,10-tetraazacyclododecanetetraacetic  
15 acid.

16. A diagnostic preparation as claimed in any one of claim 4 and claims 8 to 12, wherein the complex salt (i) is the sodium salt of the gadolinium (III) complex of 1,4,8,11-tetraazacyclotetradecanetetraacetic  
20 acid.

17. A diagnostic preparation as claimed in claim 8, substantially as described in any one of Examples 6 to 13 herein.



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18. A diagnostic preparation as claimed in any one of claims 4, 5 and 8 to 16, which is in a dosage form suitable for administration orally, neurally or intravasally.

5 19. An ampoule containing a diagnostic preparation as claimed in any one of claims 4, 5 and 8 to 16, in a form suitable for injection.

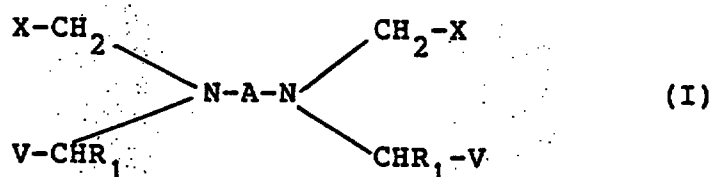
20. A process for the manufacture of a diagnostic preparation as claimed in any one of claims 4, 5 and 8  
10 to 16, wherein the complex salt (i) is dissolved or suspended in water or physiological salt solution, and is made up, if desired with the incorporation of one or more physiologically tolerable adjuncts, in a form that is suitable for intravasal or oral administration.

15 21. A process for the manufacture of a diagnostic preparation as claimed in claim 8, conducted substantially as described in any one of Examples 6 to 13 herein.

22. A physiologically tolerable, non-radioactive  
20 complex salt of the general formula I



So



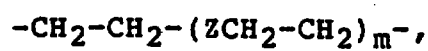
in which

X represents the radicals  $-\text{COOY}$ ,  $-\text{PO}_3\text{HY}$  or  $-\text{CONHOY}$  wherein each Y represents a hydrogen atom, a metal equivalent, the metal being selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, or a physiologically tolerable cation of an inorganic or organic base or amino acid,

and in which either

- 10 a)  $\text{R}_1$  represents in each case a hydrogen atom or methyl group,

A represents the group  $-\text{CHR}_2-\text{CHR}_3-$  or



in which

- 15  $\text{R}_2$  and  $\text{R}_3$  together represent a trimethylene group or a tetramethylene group, with the proviso that when  $\text{R}_2$  and  $\text{R}_3$  together represent a tetramethylene group, at least one Y represents a physiologically tolerable cation of an organic base or amino acid, or each represents a phenyl radical or benzyl radical,
- 20

$\underline{m}$  represents the integer 1, 2 or 3,



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and

Z represents an oxygen atom or a sulphur atom,

and

5 each V has the same meaning as X,

with the proviso that at least two of the substituents Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83,

10 or

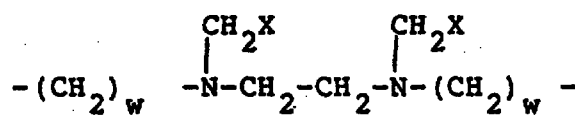
b) R<sub>1</sub> represents in each case a hydrogen atom,

A represents the group -CH<sub>2</sub>-CH<sub>2</sub>-

and

both V's together represent the group

15



in which

X has the meanings given above

and

w represents the integer 1, 2 or 3,

20 with the proviso that at least two of the substituents Y are metal equivalents selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83.



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23. A physiologically tolerable complex salt as claimed in claim 22, wherein at least one of the substituents Y is a physiologically tolerable cation of an organic base or amino acid.

5 24. Any physiologically tolerable complex salt as claimed in claim 22 specified in any one of the Examples herein.

25. The di-N-methylglucamine salt of the manganese (II) complex of trans-1,2-cyclohexylenediaminetetraacetic acid.

10 26. The N-methylglucamine salt of the gadolinium (III) complex of 1,4,7,10-tetraazacyclododecanetetraacetic acid.

27. The sodium salt of the gadolinium (III) complex of 1,4,7,10-tetraazacyclododecanetetraacetic acid.

15 28. The sodium salt of the gadolinium (III) complex of 1,4,8,11-tetraazacyclotetradecanetetraacetic acid.

29. A process for the manufacture of a physiologically tolerable complex salt as claimed in any one of claims 22 to 28, substantially as described herein.

20 30. The use of a physiologically tolerable complex salt as claimed in any one of claims 24 to 28, for the



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manufacture of a preparacion for a method of diagnosis  
of the human or animal body by NMR diagnosis, X-ray  
diagnosis or ultra-sound diagnosis.

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