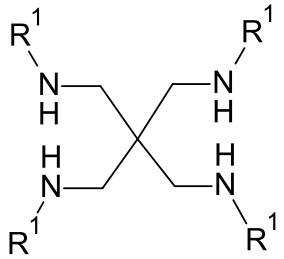
CLAIMS

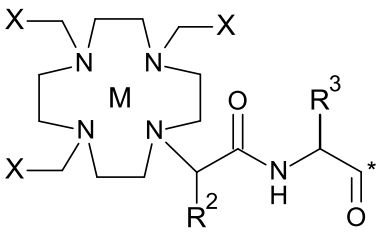
1. A liquid pharmaceutical formulation comprising a DO3A-derived tetra-chelate of general formula (I):



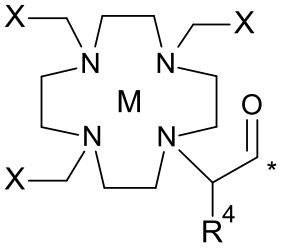
(I) ,

wherein

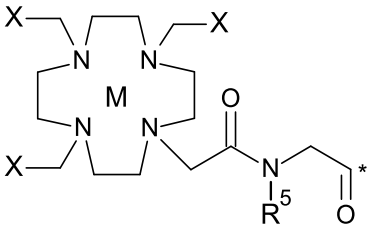
R^1 represents a group selected from:



,



, and



,

wherein group * indicates the point of attachment of said group with the rest of the molecule,

R^2, R^3, and R^4 independently of each other represents a hydrogen atom or a group selected from:

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_1-C_2-alkoxy)-(C_2-C_3-alkyl)-, and phenyl,

wherein said C_1-C_6-alkyl group is optionally substituted, identically or differently, with a phenyl substituent, which phenyl substituent is optionally substituted, one, two or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy, and

wherein said phenyl group is optionally substituted, one, two, or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy,

R^5 represents a group selected from:

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_1-C_2-alkoxy)-(C_2-C_3-alkyl)-, and phenyl,

wherein said C_1-C_6-alkyl group is optionally substituted, identically or differently, with a phenyl substituent, which phenyl substituent is optionally substituted, one, two or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy, and

wherein said phenyl group is optionally substituted, one, two, or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy,

X represents a group C(=O)OH or $C(=O)O^-$,

and

M represents Gd^{3+},

or a stereoisomer, a tautomer or a salt thereof, or a mixture of same;

wherein the formulation further comprises a pharmaceutically acceptable solvent; and

at least one compound capable of forming a chelate with the free paramagnetic metal ion M is Ca-BT-DO3A (Calcobutrol), preferably in a range of 0.002% to 5% mol/mol (inclusive), measured as a proportion relative to a total concentration of the Gd^{3-} ion in the formulation,

wherein the DO3A-derived tetra-chelate has a concentration in the formulation in a range of 60 to 750 mmol Gd^{3-} ion/L (inclusive).

2. The formulation according to claim 1, wherein:

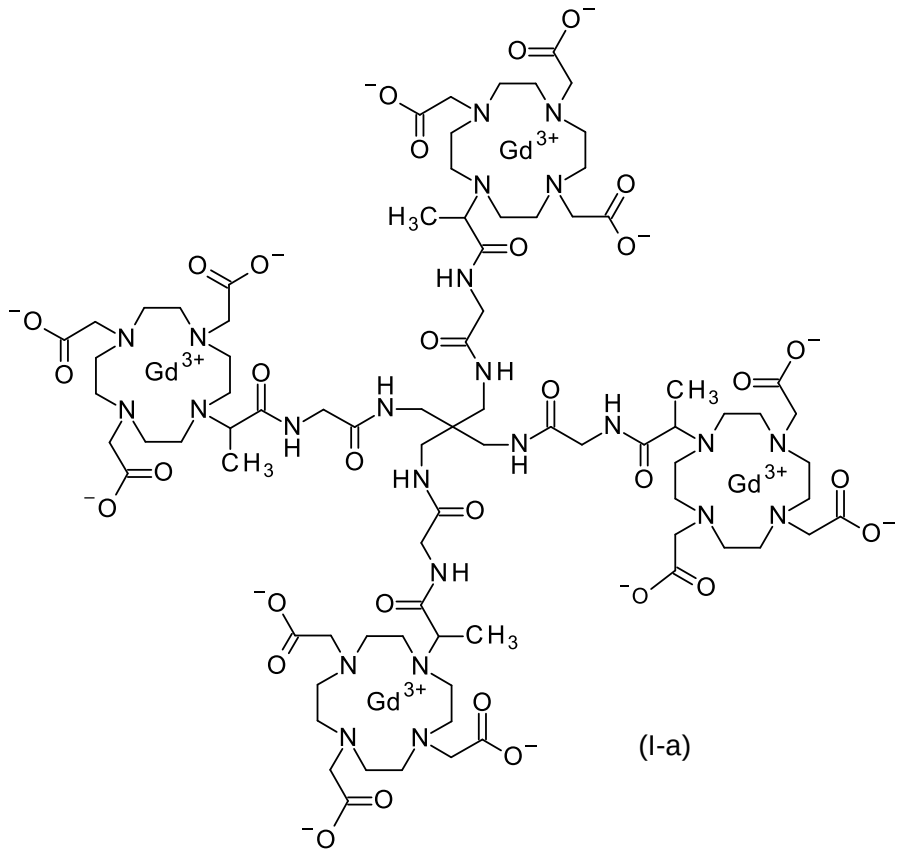
R^2 represents a hydrogen atom or a methyl group,

R^3 and R^4 each represent a hydrogen atom, and

R^5 represents a group selected from:

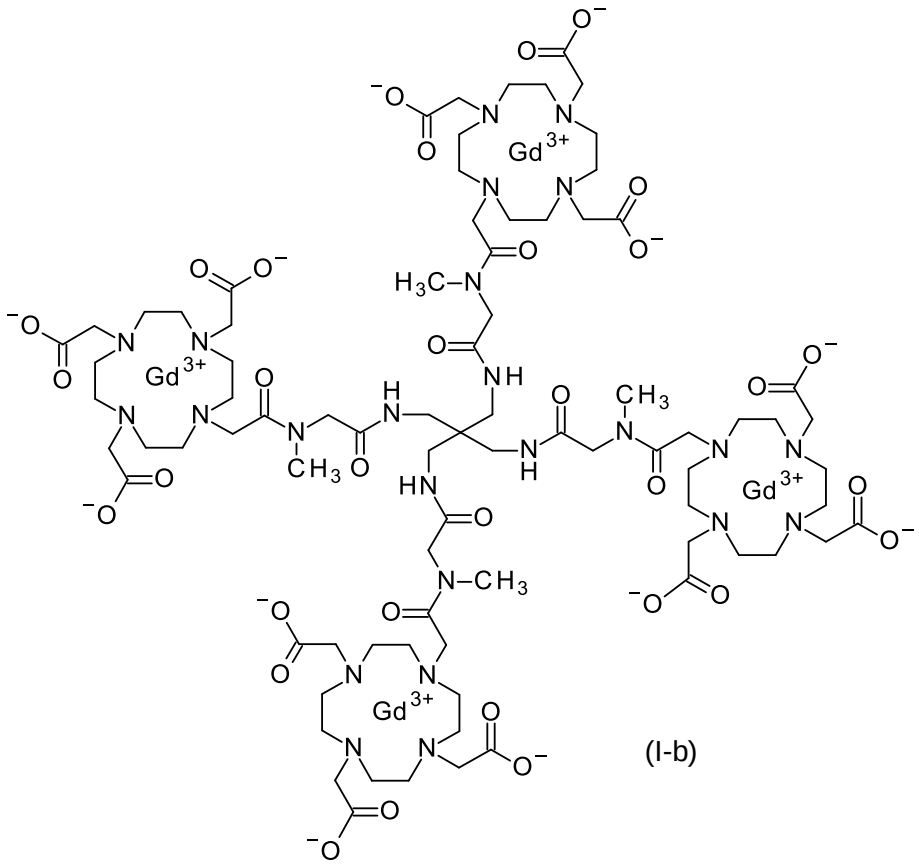
methyl, ethyl, isopropyl, 2-methylpropyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, 2-methoxyethyl, 2-ethoxyethyl, and phenyl.

3. The formulation according to claim 1, wherein the DO3A-derived tetra-chelate of formula (I) is selected from the chelates of formulae (I-a), (I-b), and (I-c):



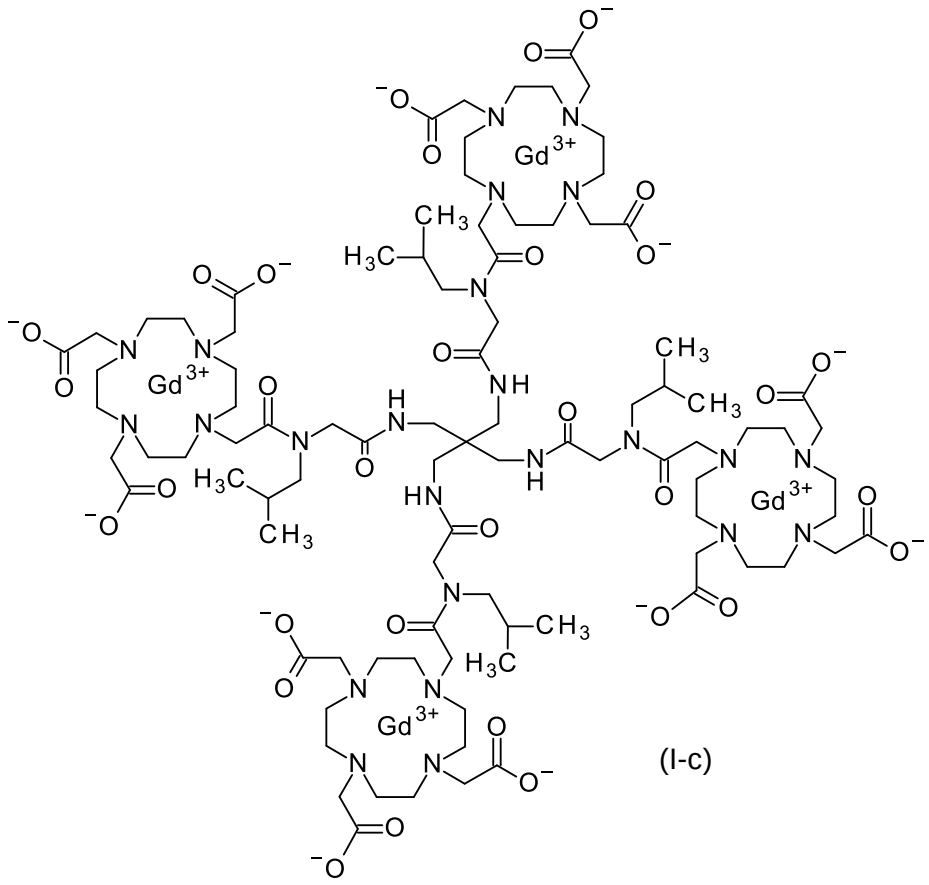
(I-a)

,



(I-b)

, and

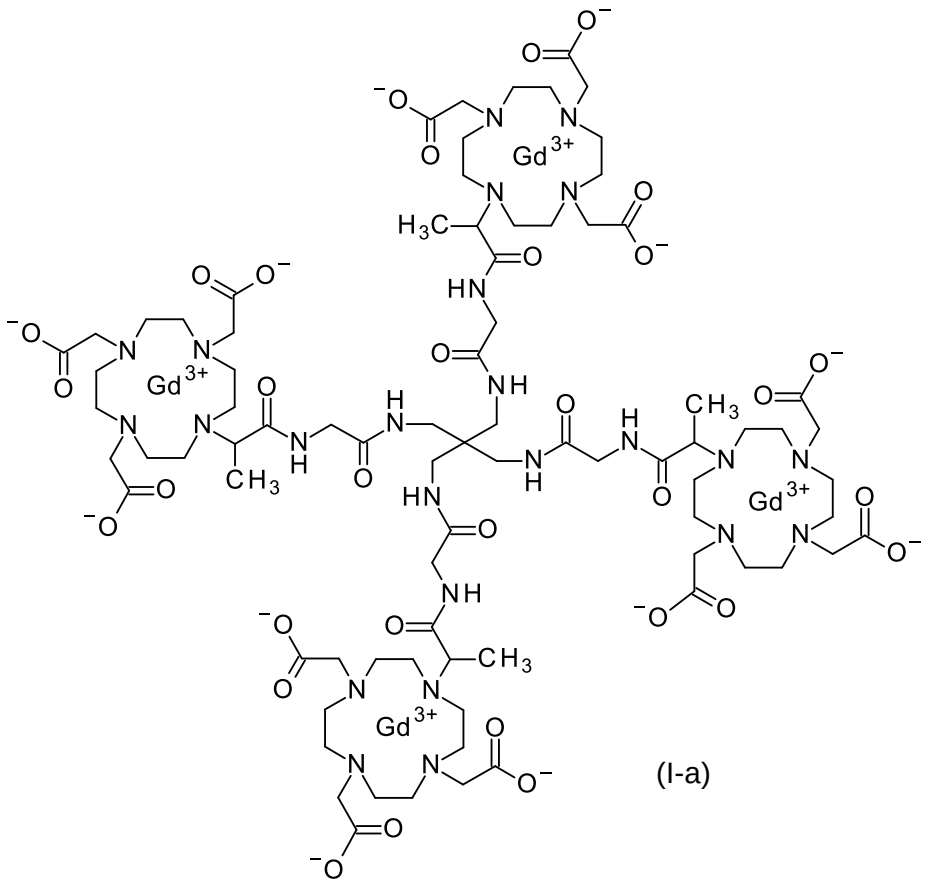


(I-c)

,

or a stereoisomer, a tautomer or a salt thereof, or a mixture of same.

4. The formulation according to claim 3, wherein the DO3A-derived tetra-chelate of formula (I) has the formula (I-a):



(I-a)

,

or a stereoisomer, a tautomer or a salt thereof, or a mixture of same.

5. The formulation according to claim 4, wherein the DO3A -derived tetra-chelate of formula (I-a) has a stereochemistry at the chiral carbon of the four methyl substituents selected from the group consisting of RRRR, SSSS, RSSS, RRSS, and RRRS stereoisomers, and racemic and diastereomeric mixtures of any thereof.

6. The formulation according to claim 1, wherein the formulation has a concentration of a free paramagnetic Gd^{3+} of less than or equal to 5 ppm (m/v).

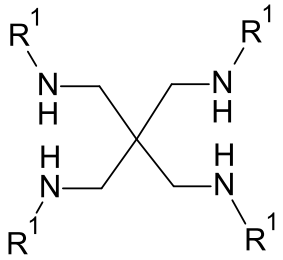
7. The formulation according to claim 1, wherein the formulation has a pH in a range of 4.5 to 8.5 (inclusive).

8. The formulation according to claim 1, further comprising a buffer, wherein the buffer is selected from the group consisting of a citrate buffer, a lactate buffer, an acetate buffer, a tartrate buffer, a malate buffer, a maleate buffer, a phosphate buffer, a succinate buffer, an ascorbate buffer, a carbonate buffer, a trometamol (TRIS, 2-amino-2-(hydroxymethyl)propane-1,3-diol) buffer, a HEPES (2-[4-(2-hydroxyethyl)-1-piperazine] ethanesulfonic acid) buffer and an MES (2-morpholinoethanesulfonic acid) buffer and mixtures thereof.

9. A process for preparing a liquid pharmaceutical formulation, the process comprising the following steps:

providing a pharmaceutically acceptable solvent;

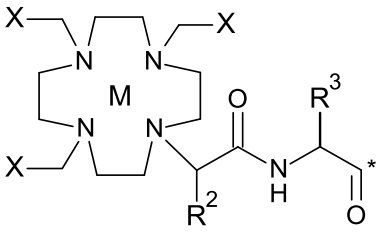
dissolving a DO3A-derived tetra-chelate of formula (I):



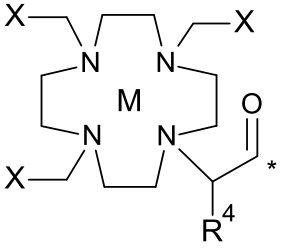
(I) ,

wherein

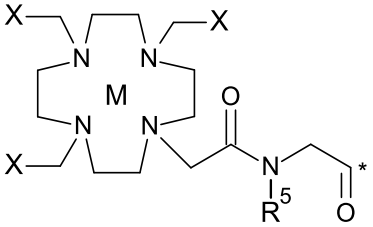
R^1 represents a group selected from:



,



, and



,

wherein group * indicates the point of attachment of said group with the rest of the molecule,

R^2, R^3, and R^4 independently of each other represents a hydrogen atom or a group selected from:

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_1-C_2-alkoxy)-(C_2-C_3-alkyl)-, and phenyl,

wherein said C_1-C_6-alkyl group is optionally substituted, identically or differently, with a phenyl substituent, which phenyl substituent is optionally substituted, one, two or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy, and

wherein said phenyl group is optionally substituted, one, two, or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy,

R^5 represents a group selected from:

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_1-C_2-alkoxy)-(C_2-C_3-alkyl)-, and phenyl,

wherein said C_1-C_6-alkyl group is optionally substituted, identically or differently, with a phenyl substituent, which phenyl substituent is optionally substituted, one, two or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy, and

wherein said phenyl group is optionally substituted, one, two, or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy,

X represents a group C(=O)OH or $C(=O)O^-$,

and

M represents Gd^{3+},

or a stereoisomer, a tautomer or a salt thereof, or a mixture of same,

in the pharmaceutically acceptable solvent in sufficient amount to produce a solution of the formulation having a concentration of DO3A-derived tetra-chelate of formula (I) in a range of 60 to 750 mmol paramagnetic Gd^{3-} ion/L (inclusive), and

dissolving at least one compound capable of forming a chelate with Gd^{3+} in sufficient amount to produce a solution having a formulation having a concentration in a range of 0.002% to 5% mol/mol (inclusive) with reference to the total concentration of the Gd^{3+} ion in the formulation, wherein the compound capable of forming a chelate with Gd^{3+} is Ca-BT-DO3A (Calcobutrol).

10. The process according to claim 9, further comprising one or more additional steps selected from the group consisting of:

dissolving a buffer in the pharmaceutically acceptable solvent or the solution, thereby obtaining a buffered solution and adjusting the pH of the buffered solution to a pH in a range of 7.6 to 8.2 (inclusive);

dissolving the Ca-BT-DO3A (Calcobutrol) in the solution;

dissolving an isotonicity agent in the solution;

adjusting the pH of the solution to a pH in a range of 4.5 to 8.5 (inclusive);

adjusting the concentration of the DO3A-derived tetra-chelate of the formula (I) by addition of an additional amount of the pharmaceutically acceptable solvent; and

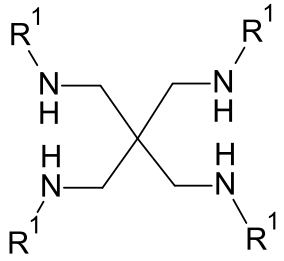
sterilizing the solution.

11. A process for preparing a liquid pharmaceutical formulation, the process comprising the following steps:

providing a pharmaceutically acceptable solvent;

dissolving Ca-BT-DO3A (Calcobutrol) in the pharmaceutically acceptable solvent; and

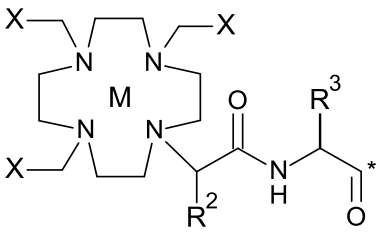
dissolving a DO3A-derived tetra-chelate of formula (I):



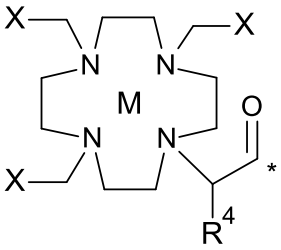
(I) ,

wherein

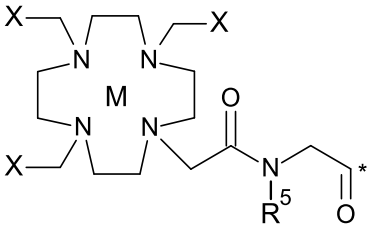
R^1 represents a group selected from:



,



, and



,

wherein group * indicates the point of attachment of said group with the rest of the molecule,

R^2, R^3, and R^4 independently of each other represents a hydrogen atom or a group selected from:

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_1-C_2-alkoxy)-(C_2-C_3-alkyl)-, and phenyl,

wherein said C_1-C_6-alkyl group is optionally substituted, identically or differently, with a phenyl substituent, which phenyl substituent is optionally substituted, one, two or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy, and

wherein said phenyl group is optionally substituted, one, two, or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy,

R^5 represents a group selected from:

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_1-C_2-alkoxy)-(C_2-C_3-alkyl)-, and phenyl,

wherein said C_1-C_6-alkyl group is optionally substituted, identically or differently, with a phenyl substituent, which phenyl substituent is optionally substituted, one, two or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy, and

wherein said phenyl group is optionally substituted, one, two, or three times, identically or differently, with a group selected from:

a halogen atom, C_1-C_3-alkyl, C_1-C_3-haloalkyl, and C_1-C_3-alkoxy,

X represents a group C(=O)OH or $C(=O)O^-$,

and

M represents Gd^{3+};

or a stereoisomer, a tautomer or a salt thereof, or a mixture of same,

in the pharmaceutically acceptable solvent in sufficient amount to produce a final solution having a formulation having a concentration of the DO3A-derived tetra-chelate of formula (I) in a range of 1 to 1000 mmol Gd^{3+} /L (inclusive), and

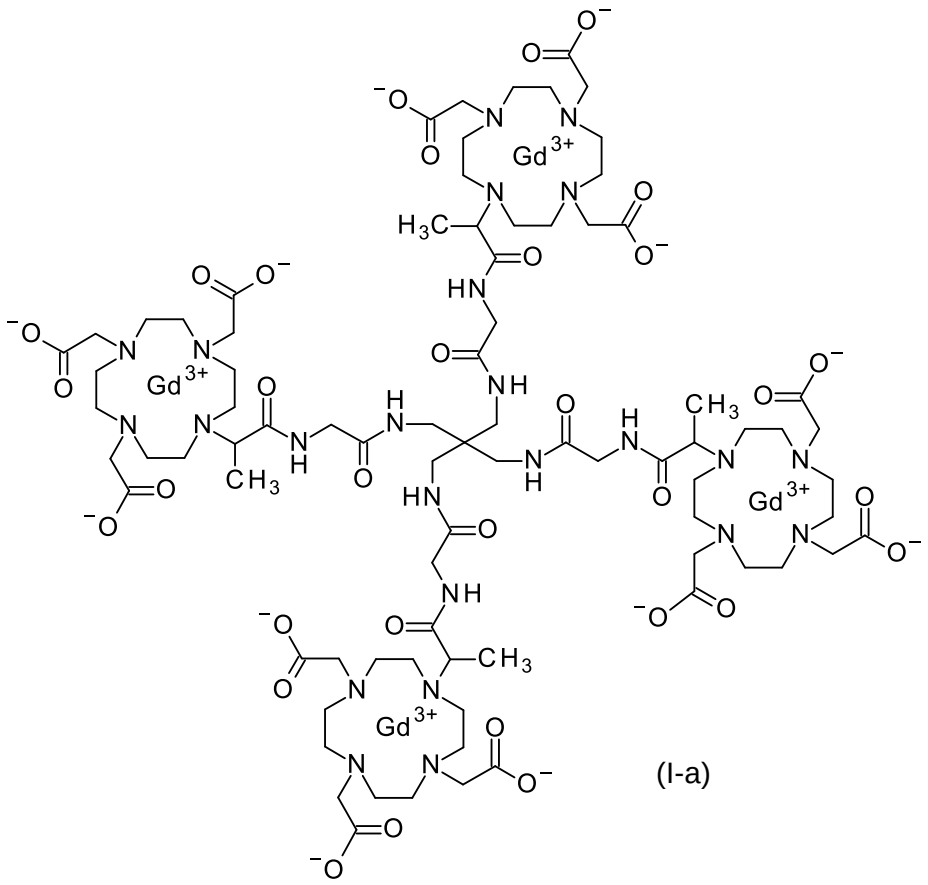
wherein the Ca-BT-DO3A is dissolved in the pharmaceutically acceptable solvent in sufficient amount to produce a solution having a concentration in a range of 0.002% to 5% mol/mol (inclusive) with reference to the total concentration of the Gd^{3+} ion.

12. The process according to claim 11, further comprising:

dissolving an amount of Ca-BT-DO3A in a range of 0.002% to 5% mol/mol (inclusive) with reference to the total concentration of the Gd^{3+} in the formulation in the pharmaceutically acceptable solvent to form a first solution; and

dissolving the DO3A-derived tetra-chelate of formula (I) in the first solution in sufficient amount to produce a final solution having a liquid pharmaceutical formulation having a concentration of the DO3A-derived tetra-chelate of formula (I) in a range of 1 mmol paramagnetic metal ion/L to 1000 mmol Gd^{3+}/L (inclusive).

13. The process according to claim 11, wherein the DO3A-derived tetra-chelate is the Gd_4-DO3A-derived tetra-chelate of formula (I-a):



(I-a)

,

or a stereoisomer, a tautomer or a salt thereof, or a mixture of same, wherein the Gd_4 -DO3A-derived tetra-chelate of formula (I-a) is dissolved in sufficient amount to produce a liquid pharmaceutical formulation having a concentration of the Gd_4 -DO3A-derived tetra-chelate of formula (I-a) in the range of 1 mmol Gd^{3+} /L to 1000 mmol Gd^{3+} /L (inclusive).

14. The process according to claim 12, wherein dissolving an amount of the CaBT-DO3A (Calcobutrol) comprises:

dissolving an amount of the Ca-BT-DO3A in the range of 0.002% to 5% mol/mol (inclusive) with reference to the total concentration of the Gd^{3+} ion in the formulation in the pharmaceutically acceptable solvent or an aqueous buffer solution to provide a first solution.