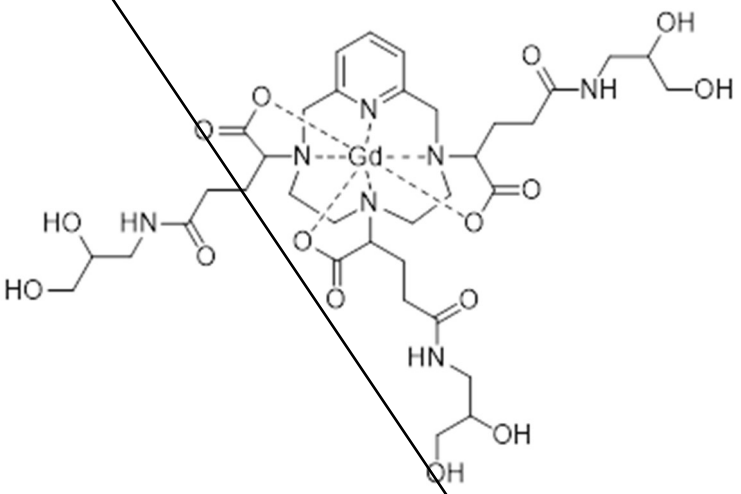
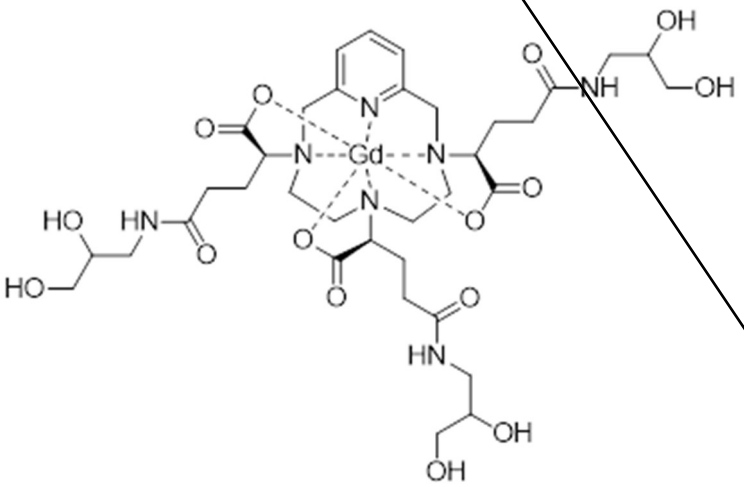
CLAIMS

1. Complex of formula (II) below:

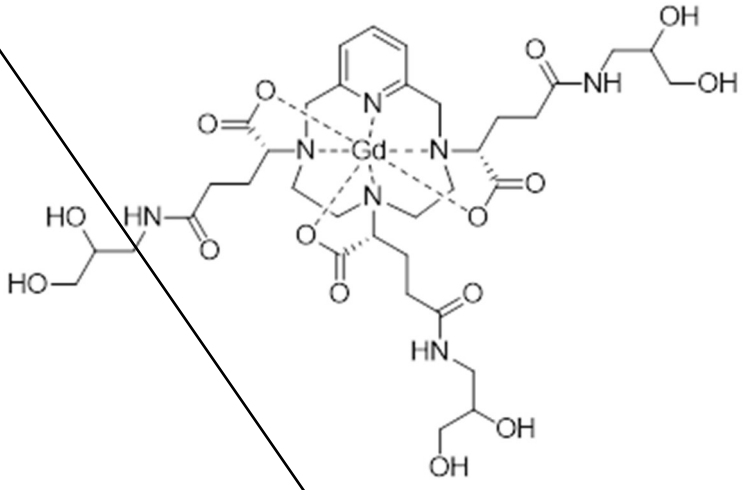


(II)

constituted of at least 90% of a diastereoisomeric excess comprising a mixture of isomers II-RRR and II-SSS of formulae:



(II-SSS),



(II-RRR).

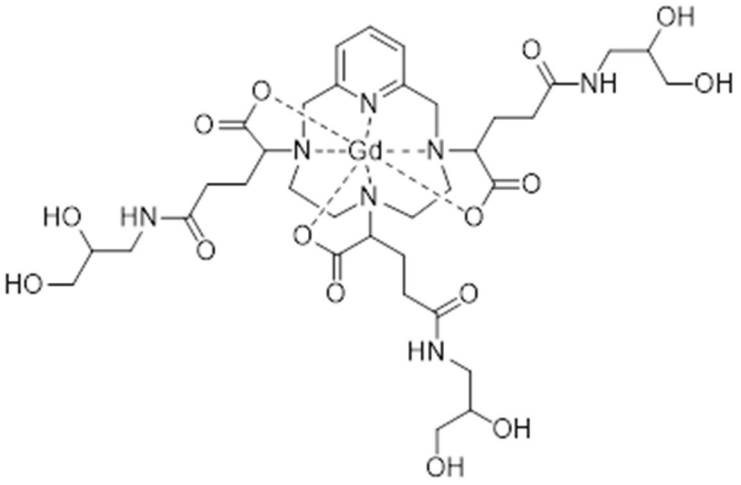
2. Composition comprising the complex according to Claim 1 and a free macrocyclic ligand, and advantageously having a concentration of free gadolinium of less than 1 ppm (m/v).

3. Composition according to Claim 2, characterized in that it comprises between 0.002 and 0.4 mol/mol% of free macrocyclic ligand relative to the complex of formula (II).

4. Composition according to Claim 2 or 3, characterized in that the free macrocyclic ligand is selected from the group constituted of DOTA, NOTA, DO3A, BT-DO3A, HP-DO3A, PCTA, DOTA-GA and derivatives thereof.

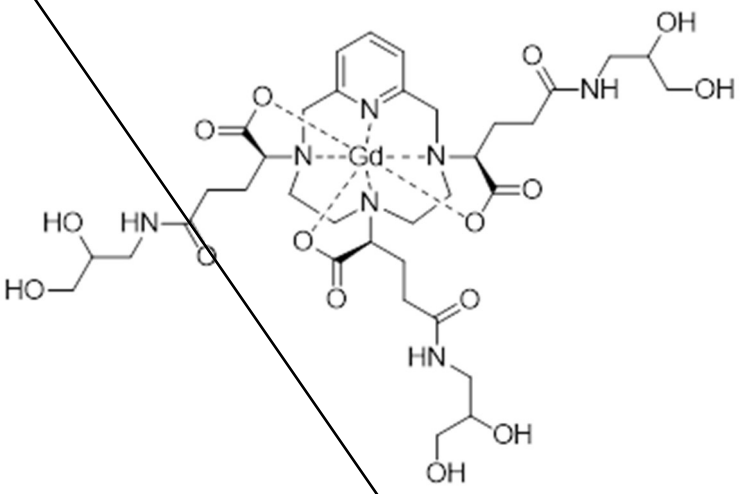
5. Composition according to Claim 4, characterized in that the free macrocyclic ligand is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

6. Process for purifying the complex of formula (II) below:

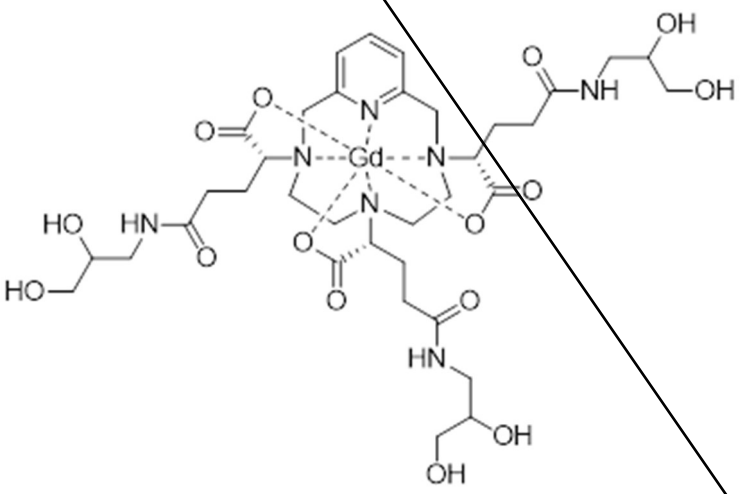


(II)

constituted of at least 80% of a diastereoisomeric excess comprising a mixture of isomers II-RRR and II-SSS of formulae:



(II-SSS),



(II-RRR),

comprising:

1) the combination of the following two steps:

1b) passage through ion-exchange resin(s), and

1c) ultrafiltration of said complex, and

2) isolation of the purified complex thus obtained in solid form.

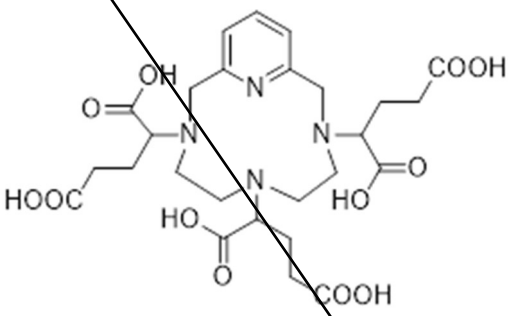
7. Process according to Claim 6, characterized in that steps 1b) and 1c) are also combined with a nanofiltration step 1a).

8. Process according to Claim 6 or 7, characterized in that the steps 1a), when it is present, 1b) and 1c) are performed in this order.

9. Process according to any one of Claims 6 to 8, characterized in that step 2) comprises atomization.

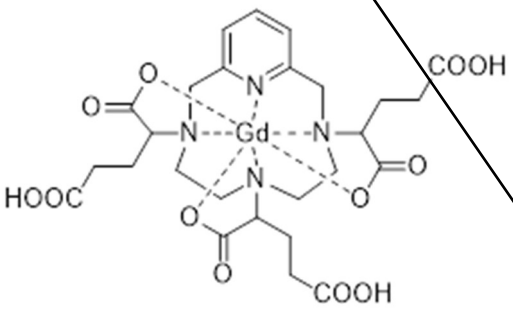
10. Process according to any one of Claims 6 to 9, characterized in that the complex of formula (II) constituted of at least 80% of a diastereoisomeric excess comprising a mixture of isomers II-RRR and II-SSS on which the purification process is performed was obtained previously via the following successive steps:

a) complexation of the hexaacid of formula (III) below:



(III)

with gadolinium to obtain the hexaacid gadolinium complex of formula (I) below:



(I),

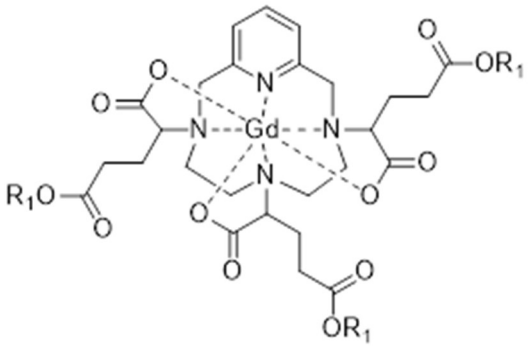
b) isomerization by heating the hexaacid gadolinium complex of formula (I) in an aqueous solution at a pH of between 2 and 4, to obtain a diastereoisomerically enriched complex constituted of at least 80% of a diastereoisomeric excess comprising a mixture of the isomers I-RRR and I-SSS of said hexaacid gadolinium complex of formula (I), and

c) formation, starting with the diastereoisomerically enriched complex obtained in step b), of the complex of formula (II), by reaction with 3-amino-1,2-propanediol.

11. Process according to Claim 10, characterized in that:

- on conclusion of step b), the diastereoisomerically enriched complex is isolated by crystallization, purified by recrystallization and further enriched by selective decomplexation of the diastereoisomers of the complex of formula (I) other than the diastereoisomers I-RRR and I-SSS, *i.e.* by selective decomplexation of the diastereoisomers I-RSS, I-SRR, I-RSR, I-SRS, I-RRS and I-SSR, and
- step c) comprises the following successive steps:

c1) formation of a triester of formula (VIII),



(VIII)

in which R_1 represents a (C_1-C_6)alkyl group,

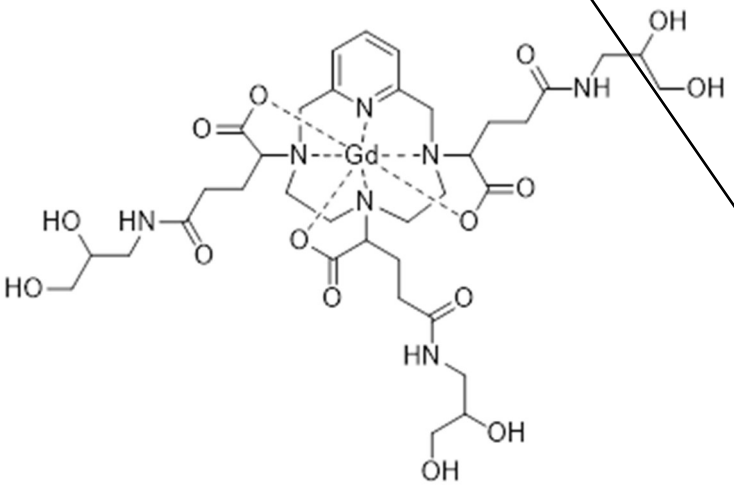
notably by reaction in the alcohol of formula R_1OH in the presence of an acid such as hydrochloric acid, and

c2) aminolysis of the triester of formula (VIII) with 3-amino-1,2-propanediol,

notably in the alcohol of formula R_1OH in the presence of an acid such as hydrochloric acid,

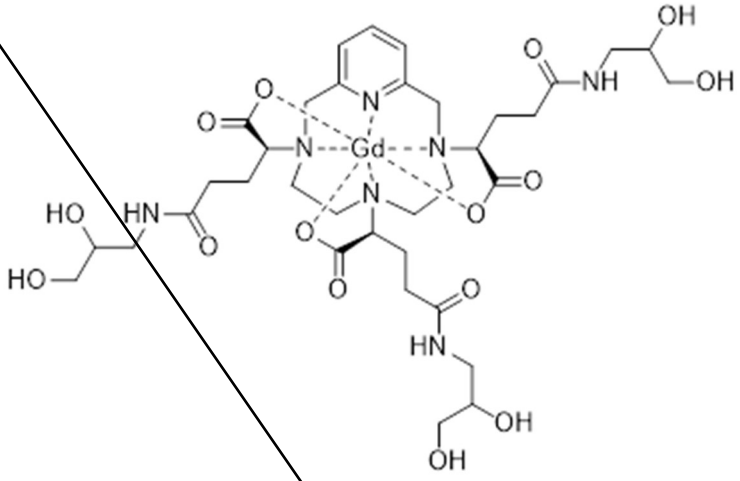
the triester of formula (VIII) not being isolated between steps c1) and c2).

12. Complex of formula (II):

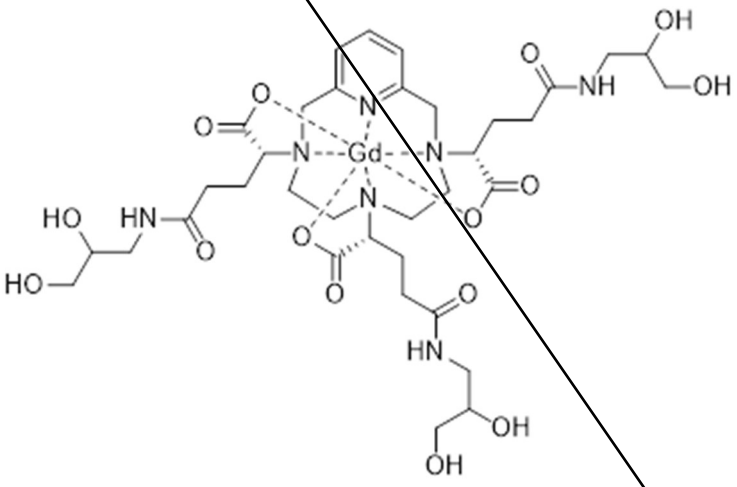


(II)

constituted of at least 80% of a diastereoisomeric excess comprising a mixture of isomers II-RRR and II-SSS of formulae:



(II-SSS),



(II-RRR),

which may be obtained via the process according to any one of Claims 6 to 11.

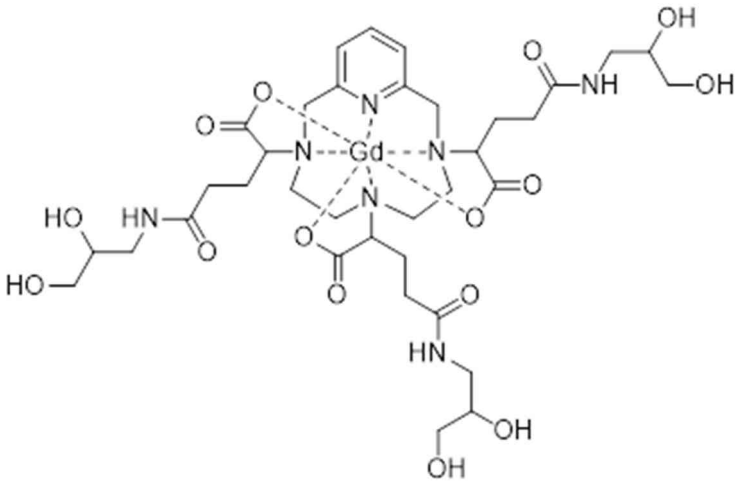
13. Complex according to Claim 12, characterized in that its degree of purity is greater than 95%.

14. Composition comprising the complex according to Claim 12 or 13 and free DOTA, and advantageously having a concentration of free gadolinium of less than 1 ppm (m/v).

15. Composition according to Claim 14, characterized in that it comprises between 0.002 and 0.4 mol/mol% of DOTA relative to the complex of formula (II).

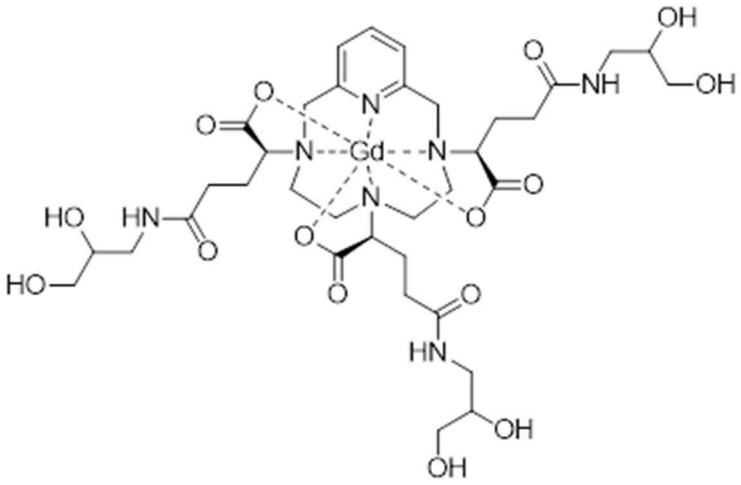
CLAIMS

1. Composition comprising the complex of formula (II) below:

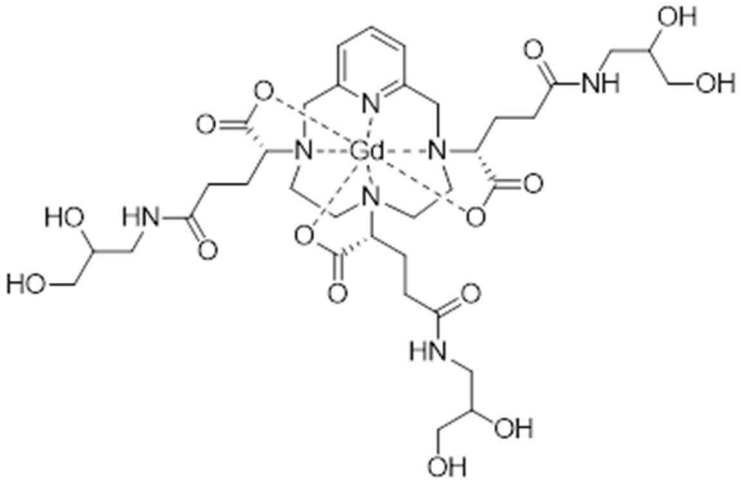


(II)

constituted of at least 80% of a diastereoisomeric excess of diastereoisomers II-RRR and II-SSS of formulae:



(II-SSS).



(II-RRR) and a free macrocyclic ligand selected from the group consisting of DOTA, NOTA, DO3A, BT-DO3A, HP-DO3A, PCTA and DOTA-GA.

2. Composition according to Claim 1, wherein the composition comprises between 0.002 and 0.4 mol/mol% of free macrocyclic ligand relative to the complex of formula (II).

3. Composition according to Claim 1 or 2, wherein the composition has a concentration of free gadolinium of less than 1 ppm (m/v).

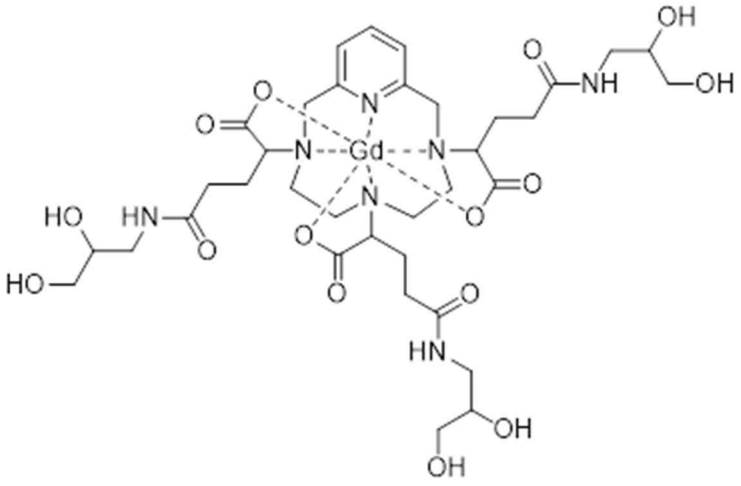
4. Composition according to Claim 3, wherein the free macrocyclic ligand is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

5. Composition according to any of claims 1 to 4, wherein the composition has a concentration of the complex of formula (II) of between 0.01 $mol.L^{-1}$ and 1.5 $mol.L^{-1}$, preferably between 0.3 and 0.6 $mol.L^{-1}$.

6. Composition according to any of claims 1 to 5, wherein the pH of the composition is between 4.5 and 8.5, preferably between 6.5 and 8.

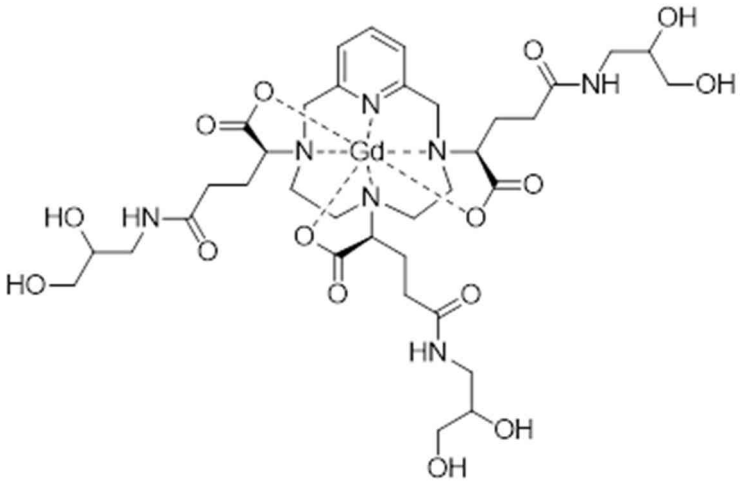
7. Composition according to any of claims 1 to 6, wherein the composition further comprises a buffer selected from the group consisting of lactate, tartrate, malate, maleate, succinate, ascorbate, carbonate, Tris (Tris(hydroxymethyl)aminomethane), HEPES (2-[4-(2-hydroxyethyl)-1-piperazine]ethanesulfonic acid) and MES (2-morpholinoethanesulfonic acid) buffers and mixtures thereof, preferably the buffer is Tris.

8. Process for purifying the complex of formula (II) below:

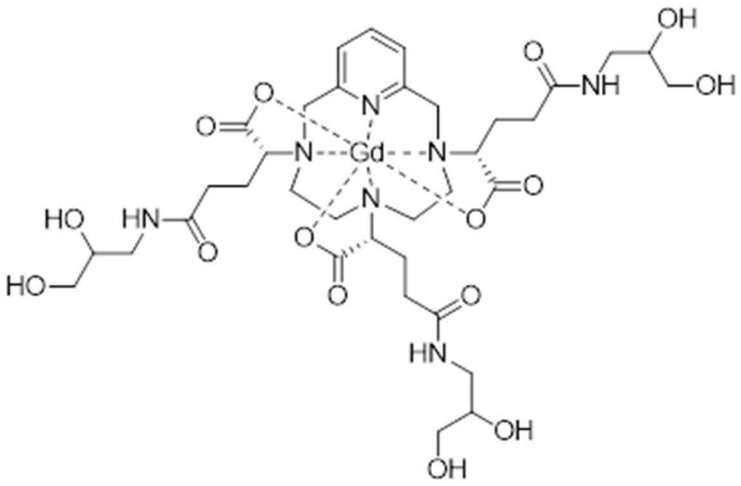


(II)

constituted of at least 80% of a diastereoisomeric excess comprising a mixture of diastereoisomers II-RRR and II-SSS of formulae:



(II-SSS),



(II-RRR),

comprising:

1) the combination of the following two steps:

1b) passage through ion-exchange resin(s), and

1c) ultrafiltration of said complex, and
2) isolation of the purified complex thus obtained in solid form.

9. Process according to Claim 8, wherein steps 1b) and 1c) are also combined with a nanofiltration step 1a).

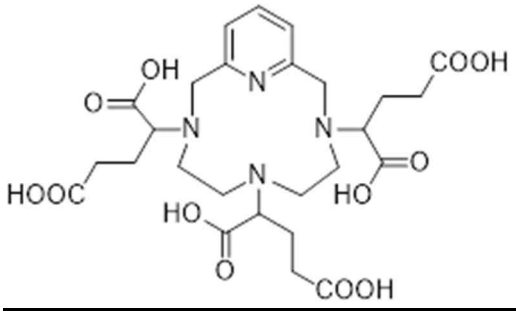
10. Process according to Claim 8 or 9, wherein the steps 1a), when it is present, 1b) and 1c) are performed in this order.

11. Process according to any one of Claims 8 to 10, wherein step 2) comprises atomization.

12. Process according to any one of Claims 8 to 11, wherein step 1b) further comprises contacting the aqueous solution of the complex of formula (II) with a cationic resin, and/or with an anionic resin.

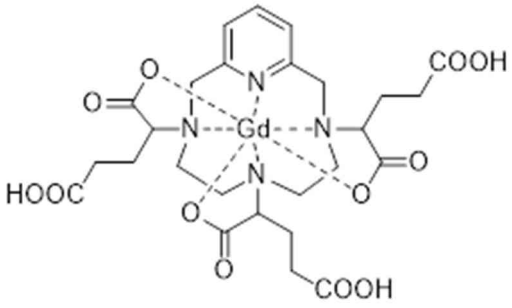
13. Process according to any one of Claims 8 to 12, wherein the process further comprises the following successive steps prior to steps 1) and 2):

a) complexation of an hexaacid of formula (III) below:



(III)

with gadolinium to obtain a hexaacid gadolinium complex of formula (I) below:



(I),

b) isomerization by heating the hexaacid gadolinium complex of formula (I) in an aqueous solution at a pH of between 2 and 4, to obtain a diastereoisomerically enriched complex

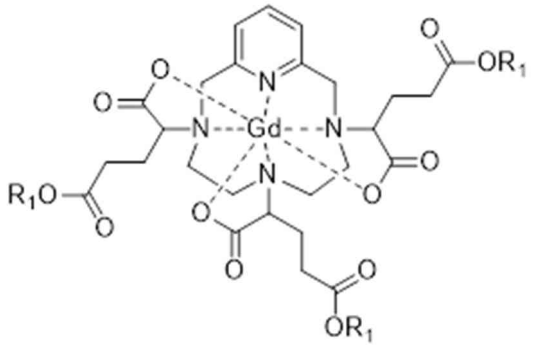
constituted of at least 80% of a diastereoisomeric excess comprising a mixture of the isomers I-RRR and I-SSS of said hexaacid gadolinium complex of formula (I), and

c) formation, starting with the diastereoisomerically enriched complex obtained in step b), of the complex of formula (II) as defined in claim 8, by reaction with 3-amino-1,2-propanediol.

14. Process according to Claim 13, wherein:

- on conclusion of step b), the diastereoisomerically enriched complex is isolated by crystallization, purified by recrystallization and further enriched by selective decomplexation of the diastereoisomers of the complex of formula (I) other than the diastereoisomers I-RRR and I-SSS, *i.e.* by selective decomplexation of the diastereoisomers I-RSS, I-SRR, I-RSR, I-SRS, I-RRS and I-SSR, and
- step c) comprises the following successive steps:

  c1) formation of a triester of formula (VIII),



(VIII)

  in which R_1 represents a (C_1-C_6)alkyl group,

  notably by reaction in the alcohol of formula R_1OH in the presence of an acid such as hydrochloric acid, and

  c2) aminolysis of the triester of formula (VIII) with 3-amino-1,2-propanediol,

  notably in the alcohol of formula R_1OH in the presence of an acid such as hydrochloric acid,

  the triester of formula (VIII) not being isolated between steps c1) and c2).