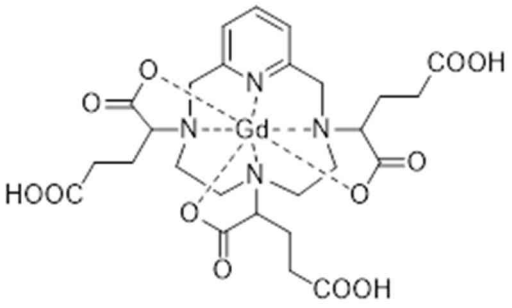
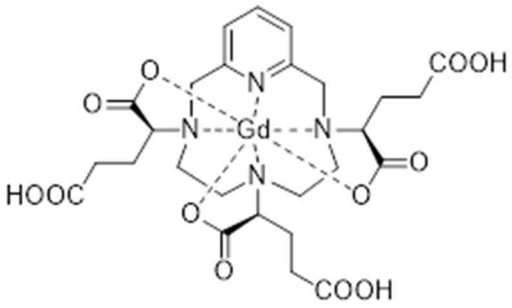
CLAIMS

1. Hexaacid gadolinium complex of formula (I):

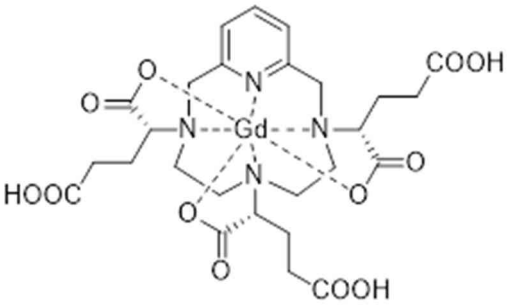


(I)

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



(I-SSS),



(I-RRR).

2. Complex according to Claim 1, characterized in that it is constituted of at least 90% of said diastereoisomeric excess.

~~3. Complex according to Claim 1 or 2, characterized in that said diastereoisomeric excess corresponds to peak 4 of the HPLC plot, characterized by a retention time of about 35.7 minutes, said plot being obtained using the following HPLC method:~~

~~• Waters Symmetry® RP18 - 250 x 4.6 mm - 5 µm column,~~

~~• analytical conditions:~~

~~- sample: aqueous solution of the complex of formula (I) at 10 mg/mL,~~

~~- column temperature: 25°C,~~

~~- sample temperature: room temperature (20-25°C),~~

~~- flow rate: 1.0 mL/min,~~

~~- injection volume: 20 µL~~

~~- UV detection: 200 nm,~~

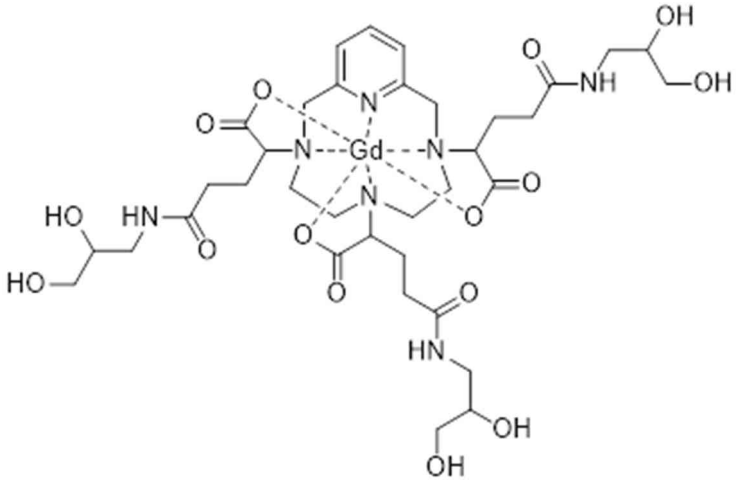
~~• mobile phase gradient (by volume):~~

~~- at 0 min, 1% acetonitrile and 99% of an aqueous solution of H_2SO_4 at 0.1% v/v,~~

~~- at 10 min, 5% acetonitrile and 95% of an aqueous solution of H_2SO_4 at 0.1% v/v,~~

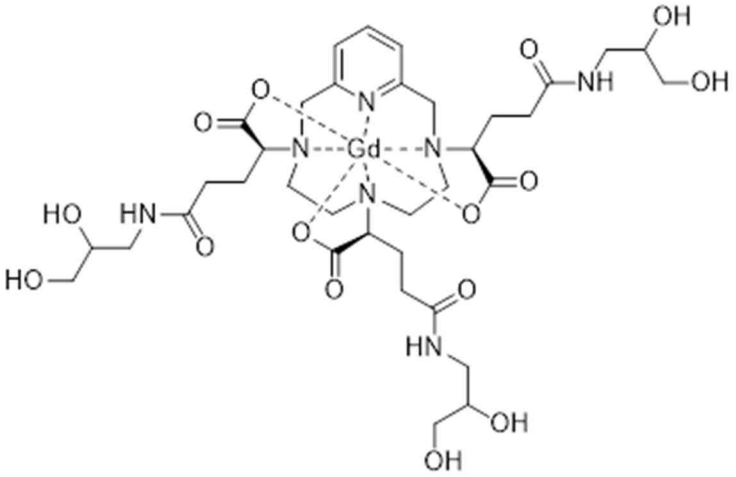
~~- at 40 min, 10% acetonitrile and 90% of an aqueous solution of H_2SO_4 at 0.1% v/v.~~

43. Complex of formula (II):

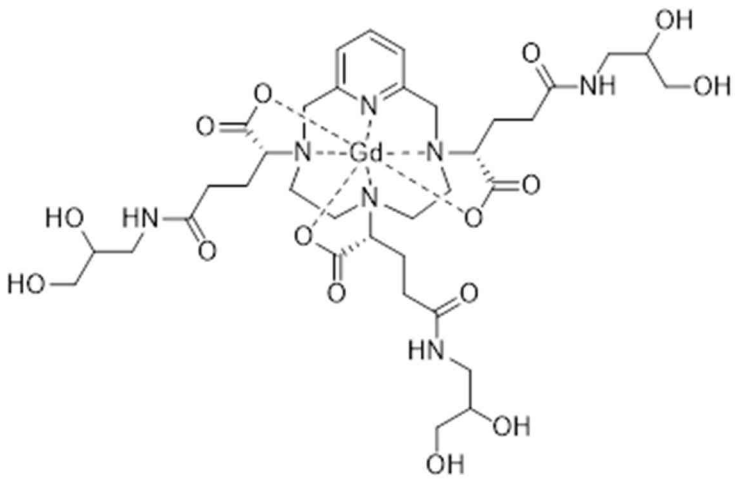


(II)

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).

~~5. Complex according to Claim 4, characterized in that said diastereoisomeric excess corresponds to peak 4 of the UHPLC plot, characterized by a retention time of about 6.3 minutes, said plot being obtained using the following UHPLC method:~~

~~• Waters Cortecs® UPLC T3 150 x 2.1 mm - 1.6 µm column,~~

~~• analytical conditions:~~

~~- sample: aqueous solution of the complex of formula (II) at 2.0 mg/mL,~~

~~- column temperature: 40°C,~~

~~- sample temperature: room temperature (20-25°C),~~

~~- flow rate: 0.3 mL/min,~~

~~- injection volume: 1 µL~~

~~- UV detection: 200 nm,~~

~~• mobile phase gradient (by volume):~~

~~- at 0 min, 1% acetonitrile and 99% of an aqueous solution of H_2SO_4 at 0.0005% v/v,~~

~~- at 3 min, 5% acetonitrile and 95% of an aqueous solution of H_2SO_4 at 0.0005% v/v,~~

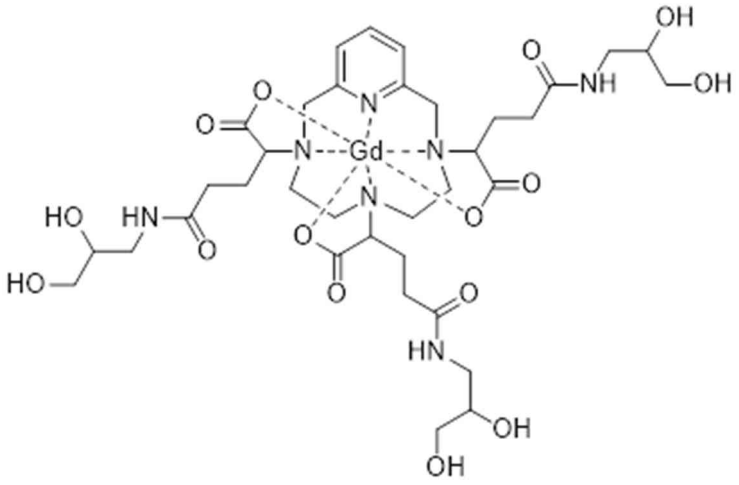
~~- at 12 min, 10% acetonitrile and 90% of an aqueous solution of H_2SO_4 at 0.0005% v/v.~~

~~6. Complex according to Claim 4 or 5, obtained by amidation starting with the hexaacid gadolinium complex of formula (I) according to any one of Claims 1 to 3 and 3-amino-1,2-propanediol.~~

4. Complex of formula (II) according to claim 3, constituted of at least 90% of a diastereoisomeric excess of isomers II-RRR and II-SSS.

5. Complex of formula (II) according to claim 3, constituted of at least 92% of a diastereoisomeric excess of isomers II-RRR and II-SSS.

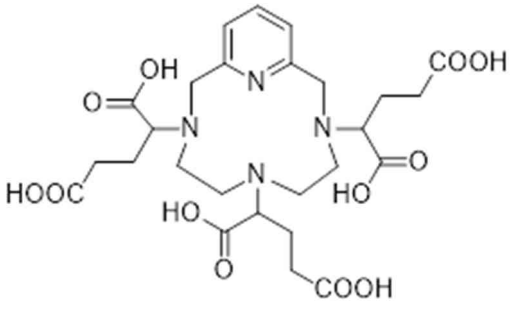
~~7~~6. Process for preparing the complex of formula (II) below:



(II)

having a diasteromeric excess of at least 80% of diastereoisomers II-RRR and II-SSS comprising 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) as defined in Claim 1,

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 diastereoisomers 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.

~~8~~7. Process according to Claim ~~7~~6, characterized in that the aqueous solution of step b) comprises acetic acid.

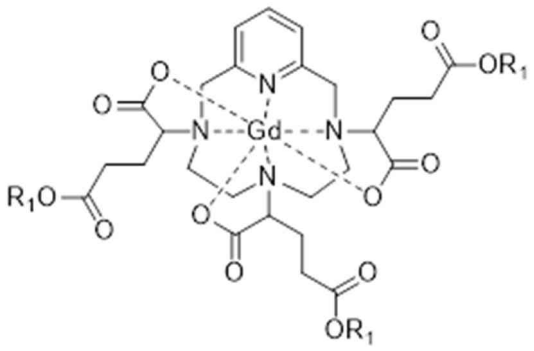
~~9~~8. Process according to Claim ~~7~~6 or ~~8~~7, characterized in that, on conclusion of step b), the diastereoisomerically enriched complex is isolated by crystallization.

~~10~~9. Process according to Claim ~~9~~8, characterized in that the diastereoisomerically enriched complex from step b) isolated by crystallization is purified by recrystallization, to obtain a diastereoisomerically enriched and purified complex.

~~11~~10. Process according to Claim ~~9~~8 or ~~10~~9, characterized in that the diastereoisomerically enriched complex from step b) is 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.

~~12~~11. Process according to any one of Claims ~~7~~6 to ~~11~~10, characterized in that step c) comprises the following successive steps:

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



(VIII)

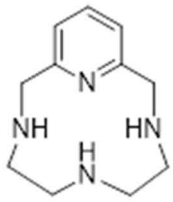
in which R_1 represents a (C_1-C_6)alkyl group, notably by reaction in the alcohol of formula R_1OH in the presence of an acid such as hydrochloric acid, and

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.

~~13~~12. Process according to Claim ~~12~~11, characterized in that the triester of formula (VIII) is not isolated between steps c1) and c2).

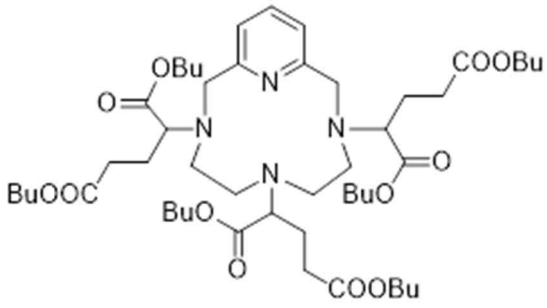
~~14~~13. Process according to Claim ~~12~~11 or ~~13~~12, characterized in that R_1 represents a methyl group.

~~15~~14. Process according to any one of Claims ~~7~~6 to ~~14~~13, characterized in that the hexaacid of formula (III) as defined in Claim ~~7~~6 is obtained by alkylation of the pyclene of formula (V):



(V)

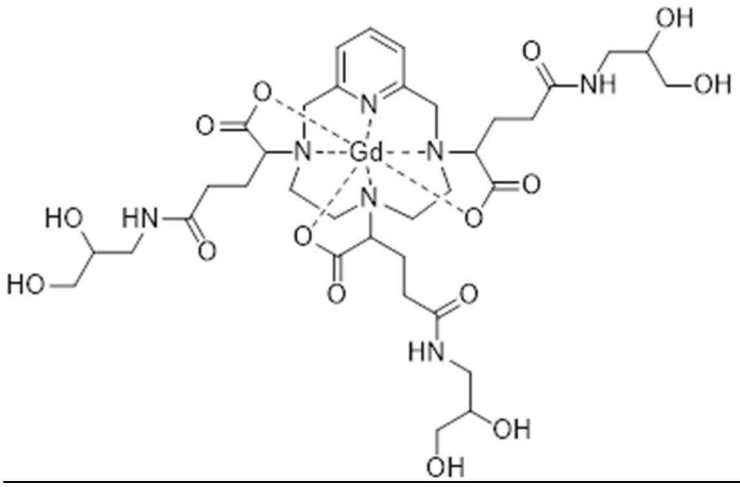
with dibutyl 2-bromoglutarate, to obtain the butyl hexaester of formula (VI)



(VI),

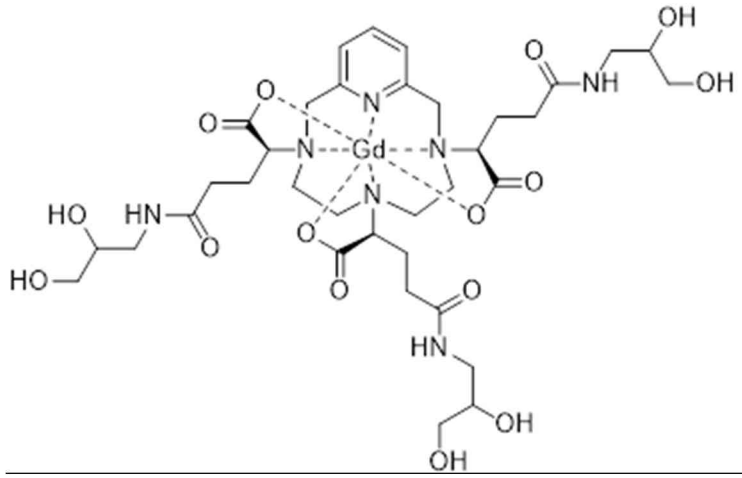
followed by a hydrolysis step, leading to said hexaacid of formula (III).

~~16. Complex of formula (II):~~

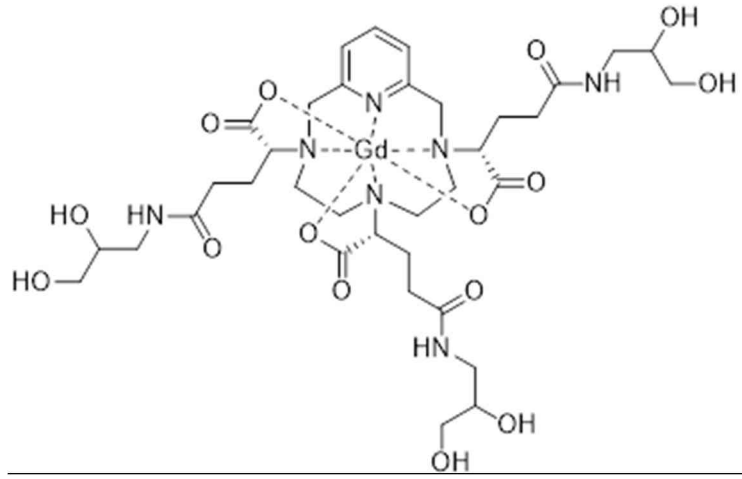


~~(II)~~

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



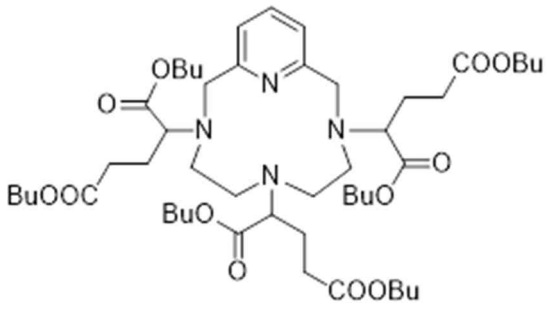
~~(II-SSS),~~



~~(II-RRR),~~

~~which may be obtained via the process according to any one of Claims 7 to 15.~~

~~17~~15. Butyl hexaester of formula (VI) below:



(VI).