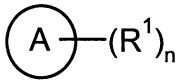
CLAIMS

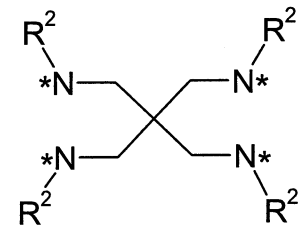
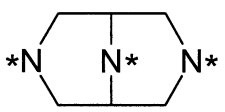
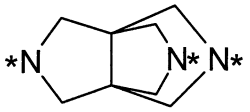
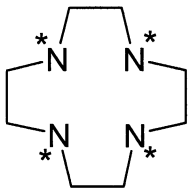
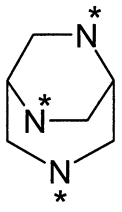
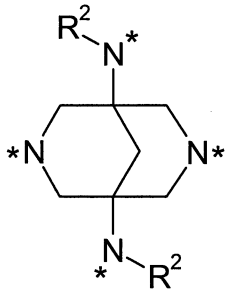
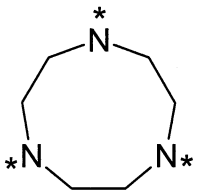
1. A compound of general formula (**I**), comprising 4, 5, 6, 7 or 8 gadolinium [4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl] groups,



(**I**),

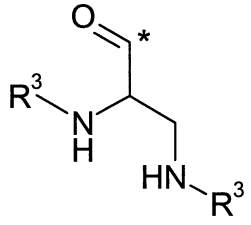
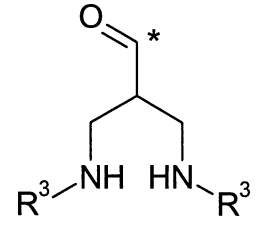
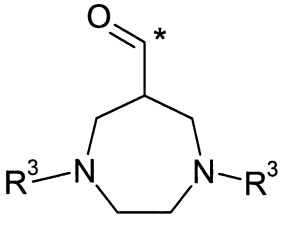
in which :

(A) represents a group selected from:


,

,

,

,

,

, and

;

in which * on the A group indicates a point of attachment of the A group with R^1 ;

R^1 represents, independently from each other, a hydrogen atom or a substituent group selected from:

R^3 ,

,

, and

,

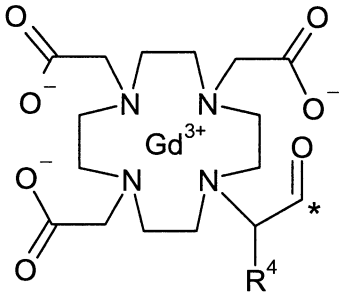
in which * on the substituent group indicates a point of attachment of the substituent group with A group,

with the proviso that zero or only one of the R^1 groups present in the compound represent a hydrogen atom;

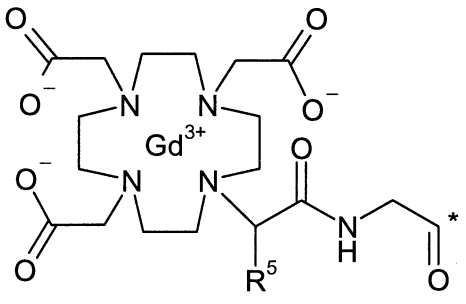
n represents an integer of 3 or 4;

R^2 represents, independently from each other, a hydrogen atom or a methyl group;

R^3 represents a group selected from:



, and



;

in which * on the R^3 group indicates a point of attachment of the R^3 group with a nitrogen on the A group or the substituent group;

R^4 represents, independently from each other, a hydrogen atom or a methyl group; and

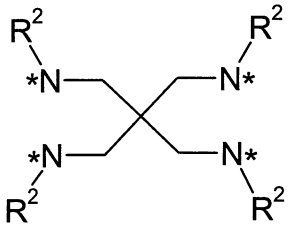
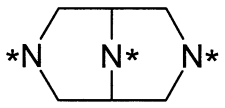
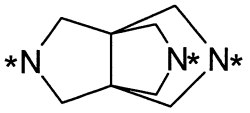
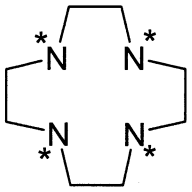
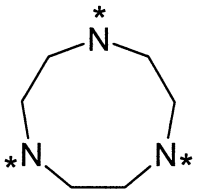
R^5 represents, independently from each other, a hydrogen atom or a methyl group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. The compound of claim 1, wherein the compound comprises 4, 5, or 6 gadolinium [4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl] R^3 groups, and wherein:



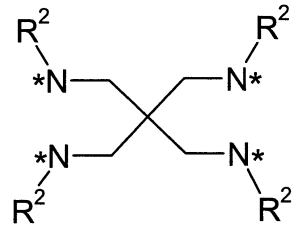
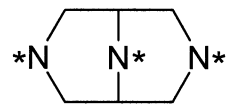
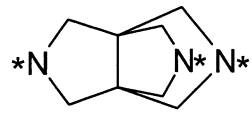
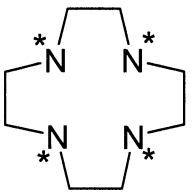
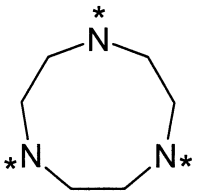
represents a group selected from:

in which * on the A group indicates a point of attachment of the A group with R^1, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

3. The compound of claim 1, wherein the compound comprises 4, 5, or 6 gadolinium [4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl] R^3 groups, and wherein:

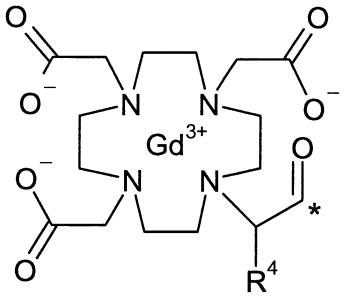
(A) represents a group selected from:

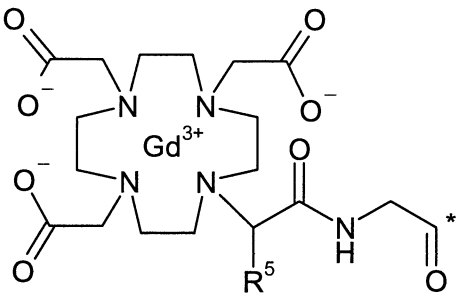






in which * on the A group indicates a point of attachment of the A group with R^1;

R^2 represents a hydrogen atom;

R^3 represents a group selected from:



, and


;

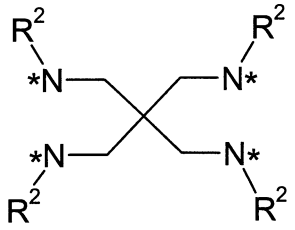
in which * on the R^3 group indicates a point of attachment of the R^3 group with a nitrogen on the A group or the substituent group; and

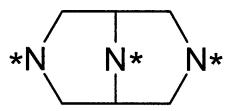
R^4 represents a hydrogen atom;

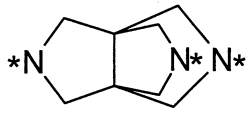
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

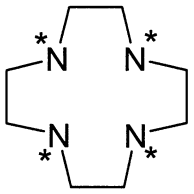
4. The compound of claim 1, wherein the compound comprises 4, 5, or 6 gadolinium [4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl] R^3 groups, and wherein:

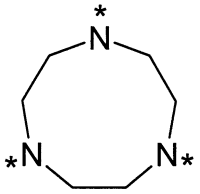
(A) represents a group selected from:



,


,


,


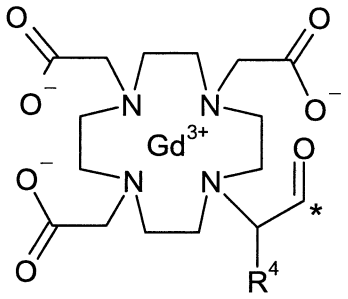
, and


;

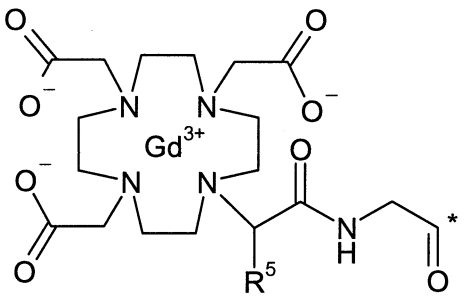
in which * on the A group indicates a point of attachment of the A group with R^1;

R^2 represents a hydrogen atom;

R^3 represents a group selected from:



, and



;

in which * on the R^3 group indicates a point of attachment of the R^3 group with a nitrogen on the A group or the substituent group;

R^4 represents a hydrogen atom;

R^5 represents a methyl group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5. The compound of claim 1, wherein the compound is selected from the group consisting of:

Tetragadolinium [4,10-bis(carboxylatomethyl)-7-{3,6,12,15-tetraoxo-16-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl}-1,4,7,10-tetraazacyclododecan-1-yl]acetate,

Tetragadolinium {4,10-bis(carboxylatomethyl)-7-[(2R,16R)-3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({(2R)-2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate,

Tetragadolinium {4,10-bis(carboxylatomethyl)-7-[(2S,16S)-3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({(2S)-2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate,

Hexagadolinium 2,2',2",2"',2"",2""',2""",2"""',2""""',2"""""',2"""""',2"

Tetragadolinium [4,10-bis(carboxylatomethyl)-7-{3,6,12,15-tetraoxo-16-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl}-1,4,7,10-tetraazacyclododecan-1-yl]acetate,

Tetragadolinium {4,10-bis(carboxylatomethyl)-7-[(2R,16R)-3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({(2R)-2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate,

Tetragadolinium {4,10-bis(carboxylatomethyl)-7-[(2S,16S)-3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({(2S)-2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate,

Tetragadolinium {4,10-bis(carboxylatomethyl)-7-[2-oxo-2-({3-({[4,7,10-tris(carboxylato-methyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl}amino)-2,2-bis[({[4,7,10-tris(carboxylato-methyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl}amino)methyl]propyl}amino)ethyl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate, and

Tetragadolinium [4,10-bis(carboxylatomethyl)-7-{2,5,11,14-tetraoxo-15-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-8,8-bis({[({[4,7,10-tris(carboxylato-methyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl}amino)acetyl]amino}methyl)-3,6,10,13-tetraazapentadec-1-yl}-1,4,7,10-tetraazacyclododecan-1-yl]acetate,

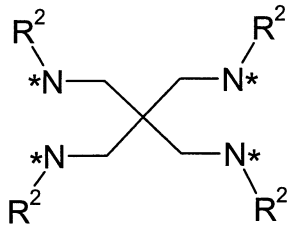
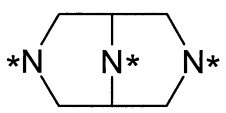
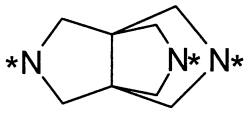
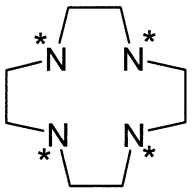
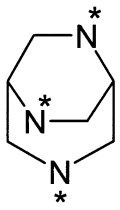
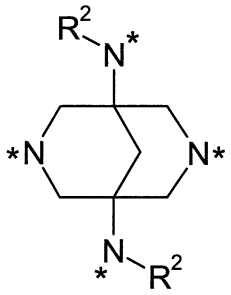
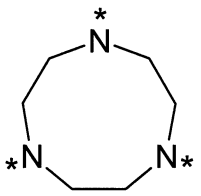
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

7. A method of preparing a compound of general formula (I-d), the method comprising: reacting a compound of formula 4,



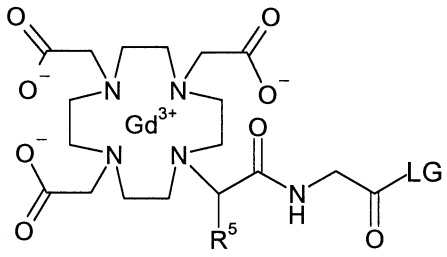
4

in which  has a structure:

where each group * represents a hydrogen atom or a salt thereof,

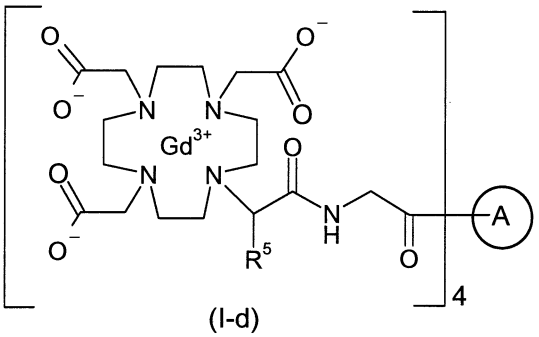
with a compound of general formula (III) :



(III)

in which R^5 is a hydrogen atom or a methyl group, and LG represents an activating leaving group selected from the group consisting of pentafluorophenol, 4-nitrophenol, 1-hydroxypyrrolidine-2,5-dione, hydroxybenzotriazole, and 3H-[1,2,3]triazolo[4,5-b]pyridine-3-ol,

to afford a compound of general formula (I-d):



(I-d)

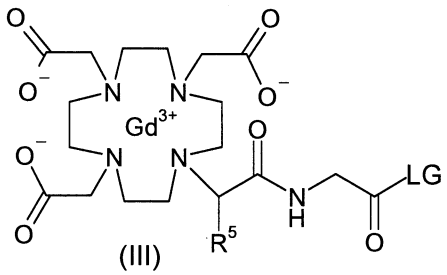
8. A method of imaging body tissue in a patient, comprising:
administering to the patient an effective amount of one or more compounds of claim 1, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, in a pharmaceutically acceptable carrier, and subjecting the patient to a magnetic resonance imaging procedure.

9. A compound of any one of claims 1 to 6, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, for use in magnetic resonance imaging.

10. Use of the compound or mixture thereof of any one of claims 1 to 6, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, for the manufacture of diagnostic agents.

11. Use of the compound or mixture thereof of any one of claims 1 to 6, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, for the manufacture of contrast agents for magnetic resonance imaging.

12. A compound of general formula (III):



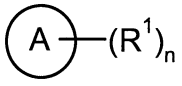
(III)

in which R^5 is a hydrogen atom or a methyl group, and LG represents an activating leaving group selected from the group consisting of pentafluorophenol, hydroxybenzotriazole, and 3H-[1,2,3]triazolo[4,5-b]pyridine-3-ol.

13. The compound of claim 1, wherein the compound is:
Tetragadolinium [4,10-bis(carboxylatomethyl)-7-{3,6,12,15-tetraoxo-16-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({2-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}methyl)-4,7,11,14-tetraazacyclododecan-2-yl}-1,4,7,10-tetraazacyclododecan-1-yl]acetate,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

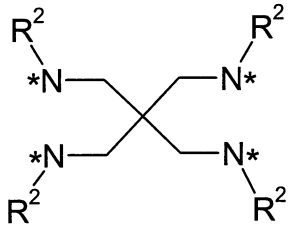
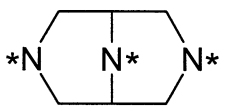
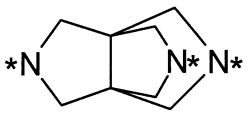
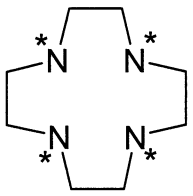
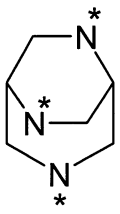
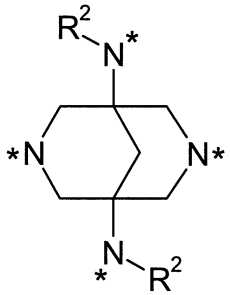
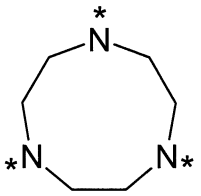
14. A compound of general formula (II), comprising:



(II),

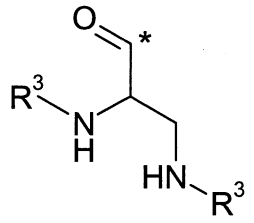
in which :

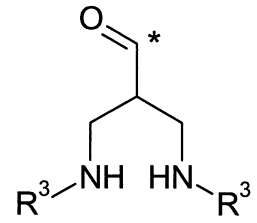
A represents a group selected from:

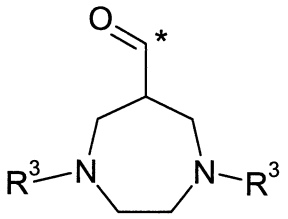

,

,

,

,

,

, and

;

in which * on the A group indicates a point of attachment of the A group with R^1;

R^1 represents, independently from each other, a hydrogen atom or a substituent group selected from:



, 

, and 

,

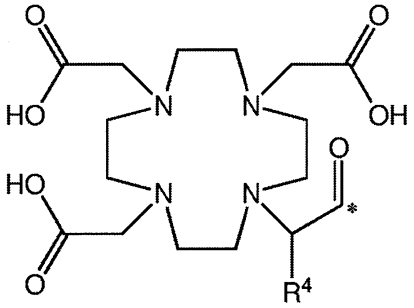
in which * on the substituent group indicates a point of attachment of the substituent group with A group,

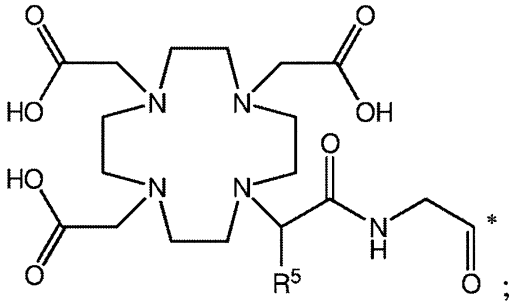
with the proviso that zero or only one of the R^1 groups present in the compound represent a hydrogen atom;

n represents an integer of 3 or 4 ;

R^2 represents, independently from each other, a hydrogen atom or a methyl group;

R^3 represents a group selected from:



, and 

;

in which * on the R^3 group indicates a point of attachment of the R^3 group with a nitrogen on the A group or the substituent group;

R^4 represents, independently from each other, a hydrogen atom or a methyl group; and

R^5 represents, independently from each other, a hydrogen atom or a methyl group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

15. The compound of claim 14, wherein the compound is selected from the group consisting of:

[4,10-bis(carboxylatomethyl)-7-{3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({2-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}methyl)-4,7,11,14-tetraazaheptadecan-2-yl}-1,4,7,10-tetraazacyclododecan-1-yl]acetate,

{4,10-bis(carboxylatomethyl)-7-[(2R,16R)-3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({(2R)-2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate,

{4,10-bis(carboxylatomethyl)-7-[(2S,16S)-3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({(2S)-2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}-methyl)-4,7,11,14-tetraazaheptadecan-2-yl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate,

2,2',2",2"',2"",2""',2"""',2""""',2"""""',2""""""',2"""""""',2""""""""',2"""""""""',2""""""""",2"""""""""',
2""""""""",2""""""""",2"""""""""'-(1,4,7-triazonane-1,4,7-triyltris{carbonyl-1,4-diazepane-6,1,4-triyl-bis[(2-oxoethane-2,1-diyl)imino(1-oxopropane-1,2-diyl)-1,4,7,10-tetraazacyclododecane-10,1,4,7-tetrayl]})octadecaacetate,

2,2',2",2"',2"",2""',2"""',2""""',2"""""',2""""""',2"""""""',2""""""""',2"""""""""'-{1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayltetrakis[(2-oxoethane-2,1-diyl)imino(1-oxopropane-1,2-diyl)-1,4,7,10-tetraazacyclododecane-10,1,4,7-tetrayl]}dodecaacetate,

2,2',2",2"',2"",2""',2"""',2""""',2"""""',2""""""',2"""""""',2""""""""',2"""""""""',2""""""""",2"""""""""',
2""""""""",2""""""""",2"""""""""'-{3,7,10-triazatricyclo[3.3.3.$0^{1,5}$]undecane-3,7,10-triyltris[carbonyl-(3,6,11,14-tetraoxo-4,7,10,13-tetraazahexadecane-8,2,15-triyl)di-1,4,7,10-tetraazacyclodo-decane-10,1,4,7-tetrayl]}octadecaacetate,

2,2',2",2"',2"",2""',2"""',2""""',2"""""',2""""""',2"""""""',2""""""""'-(3,7,9-triazabicyclo[3.3.1]nonane-3,7-diylbis{carbonyl-1,4-diazepane-6,1,4-triylbis[(2-oxoethane-2,1-diyl)-1,4,7,10-tetraazacyclododecane-10,1,4,7-tetrayl]})dodecaacetate, and

{4,10-bis(carboxylatomethyl)-7-[2-oxo-2-({3-({[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl}amino)-2,2-bis[({[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl}amino)methyl]propyl}amino)ethyl]-1,4,7,10-tetraazacyclododecan-1-yl}acetate;

[4,10-bis(carboxylatomethyl)-7-{2,5,11-14-tetraoxo-15-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-8,8-bis({[({[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl}amino)acetyl]amino}methyl)-3,6,10,13-tetraazapentadec-1-yl}-1,4,7,10-tetraazacyclododecan-1-yl]acetate, and

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

16. The compound of claim 14, wherein the compound is:
[4,10-bis(carboxylatomethyl)-7-{3,6,12,15-tetraoxo-16-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]-9,9-bis({[({2-[4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]amino}methyl)-4,7,11,14-tetraazaheptadecan-2-yl}-1,4,7,10-tetraazacyclododecan-1-yl]acetate,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.