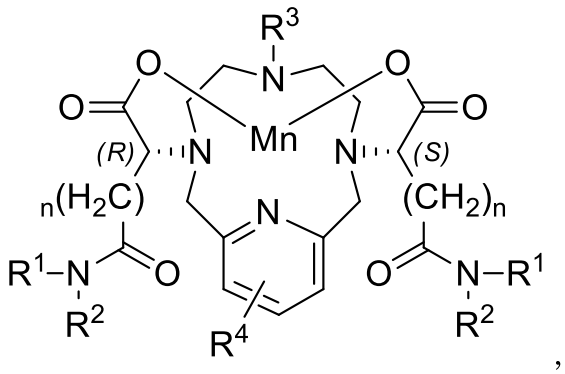
[0022] There remains a need to develop manganese contrast agents having stability that are suitable for use as contrast agents.

SUMMARY

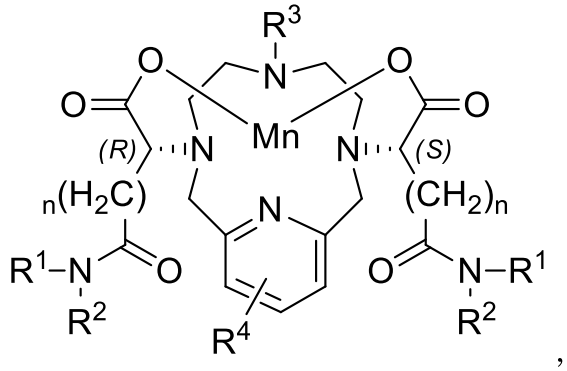
[0023] The present disclosure relates to compound of formula IA:



(IA)

or a salt or solvate thereof. In the above formula, each R^1 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety. Each R^2 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl or hydrogen. R^3 is selected from C_{1-3} alkyl or -$(CH_2)_m$-C(=0)- NR^5R^6, wherein m is an integer from 2–5, wherein R^5 and R^6 are independently selected from hydrogen, from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety. R^4 represents 0–3 substituents selected from hydroxy, $C_{1–6}$ alkyl and C_{1-6} hydroxyalkyl. Each n is an integer from 0–4.

[0023a] In an aspect, there is provided a compound of formula IA:



(IA)

or a salt or solvate thereof, wherein:

each R^1 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety;

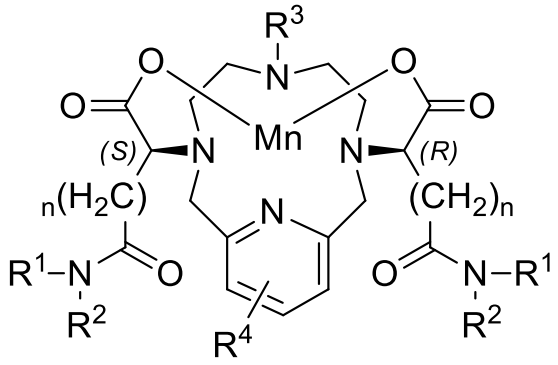
each R^2 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl or hydrogen;

R^3 is selected from C_{1-3} alkyl or -$(CH_2)_m$-C(=0)- NR^5R^6, wherein m is an integer from 2–5, wherein R^5 and R^6 are independently selected from hydrogen, from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety;

R^4 represents 0–3 substituents selected from hydroxy, $C_{1–6}$ alkyl and C_{1-6} hydroxyalkyl; and,

each n is an integer from 0–4.

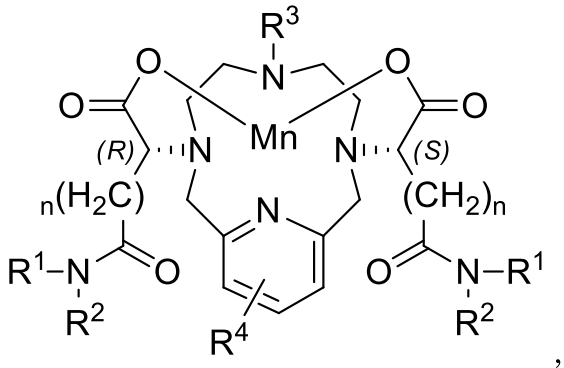
[0024] In one example, the disclosure involves composition comprising a compound of formula IA, or a salt or solvate thereof, and a pharmaceutically acceptable excipient. In one example, the composition lacks detectable amounts of a compound of Formula IB:



(IB)

[0025] where each R^1 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety. Each R^2 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl or hydrogen. R^3 is selected from C_{1-3} alkyl or -$(CH_2)_m$-C(=0)- NR^5R^6, wherein m is an integer from 2–5, wherein R^5 and R^6 are independently selected from hydrogen, from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety. R^4 represents 0–3 substituents selected from hydroxy, $C_{1–6}$ alkyl and C_{1-6} hydroxyalkyl. Each n is an integer from 0–4.

[0025a] In another aspect, there is provided a composition comprising a compound of formula IA:



(IA)

or a salt or solvate thereof, and a pharmaceutically acceptable excipient, wherein:

each R^1 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety;

each R^2 is independently selected from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl or hydrogen;

R^3 is selected from C_{1-3} alkyl or -$(CH_2)_m$-C(=0)- NR^5R^6, wherein m is an integer from 2–5, wherein R^5 and R^6 are independently selected from hydrogen, from $C_{1–20}$ hydroxyalkyl, C_{1-6} alkyl, $C_{3–6}$ aryl optionally-substituted with one or more substituents selected from halo and -C(=O)-NH-$C_{1–6}$ hydroxyalkyl, or a carbohydrate moiety;

R^4 represents 0–3 substituents selected from hydroxy, $C_{1–6}$ alkyl and C_{1-6} hydroxyalkyl; and,

each n is an integer from 0–4.

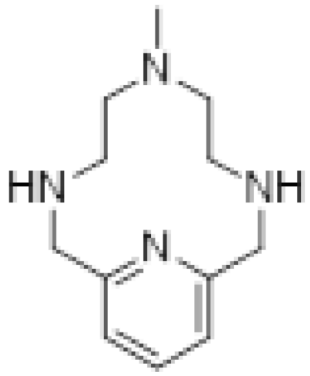
[0026] In one example, the disclosure involves a method of imaging a patient comprising administering the contrast agent, or contrast agent composition, followed by acquiring an MRI image of the patient.

[0026a] In another aspect, there is provided a method of imaging a patient comprising administering the compound as defined above to a patient in need thereof, followed by acquiring an MRI image of the patient.

[0027] In one example, the disclosure involves a method of making the imaging agent as described above. The method may involve enantioselective synthesis, or isomerization from compounds of Formula (1A) to compounds of Formula (1B).

[0027a] In another aspect, there is provided a method of enantioselective synthesis of the compound of Formula (1A) as defined above comprising:

(a) monoalkylation using a first enantiomer of 5-benzyl 1-*tert*-butyl 2-(methylsulfonyloxy) pentanedioate of a compound of formula (III)



(III);

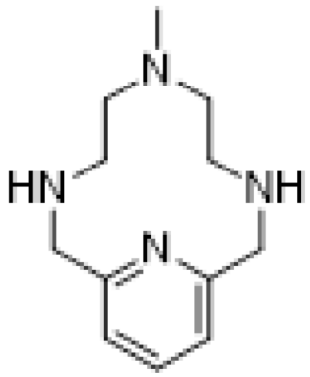
(b) followed by alkylation of the compound from step (a) with a second enantiomer of 5-benzyl 1-*tert*-butyl 2-(methylsulfonyloxy) pentanedioate, the second enantiomer being opposite the first enantiomer;

(c) reacting the product of step (b) with Mn; and

(d) reacting the product of step (c) with an aminoalcohol.

[0027b] In another aspect, there is provided a method of enantioselective synthesis of a composition comprising Formula (1A) as defined above comprising:

(a) monoalkylation using a first enantiomer of 5-benzyl 1-*tert*-butyl 2-(methylsulfonyloxy) pentanedioate of a compound of formula (III)



(III);

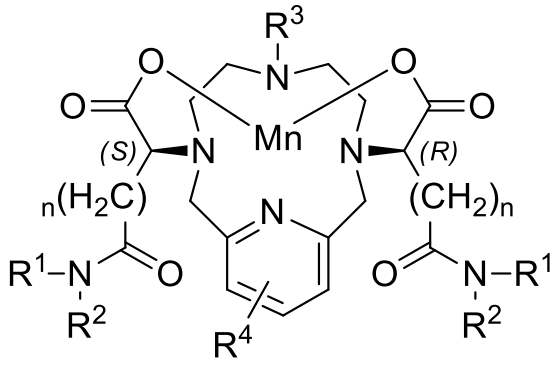
(b) followed by alkylation of the compound from step (a) with a second enantiomer of 5-benzyl 1-*tert*-butyl 2-(methylsulfonyloxy) pentanedioate, the second enantiomer being opposite the first enantiomer;

(c) reacting the product of step (b) with Mn; and

(d) reacting the product of step (c) with an aminoalcohol.

[0027c] In another aspect, there is provided a method of making the composition as defined above, wherein the method comprises:

heating a composition comprising the compound of Formula (1B):



(IB)

or a salt or solvate thereof;

wherein the heating is for a sufficient time and temperature to convert substantially all of the compound of Formula (1B) into the compound of Formula (1A).

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Fig. 1 shows the predicted stereoisomers of Mn Chelate-5.