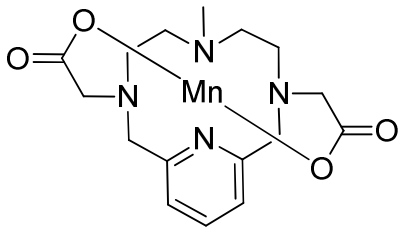
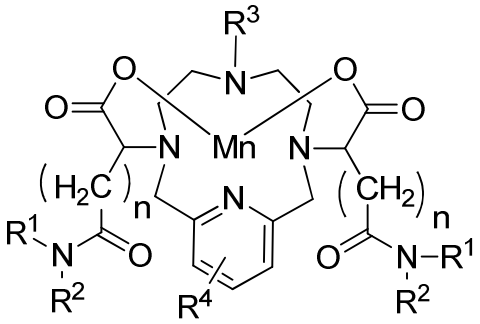
herein as “prior art Mn Chelate”):



Nevertheless, there is still scope for further manganese chelate compounds having improved and sustained kinetic stability while maintaining viable relaxation properties.

Summary

In one aspect the present disclosure provides a compound of Formula I:



(I)

or a salt or solvate thereof, wherein:

each R^1 is independently selected from the group comprising 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 the group comprising C_{1-20} hydroxyalkyl, C_{1-6} alkyl or hydrogen;

R^3 is selected from the group comprising C_{1-3} alkyl or $–(CH_2)_m$-C(=O)-NR^5R^6 wherein m is an integer from 2-5, and R^5 and R^6 are as respectively defined for R^1 and R^2;

R^4 represents 0-3 substituents selected from the group comprising

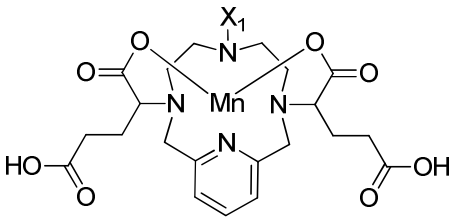
hydroxy, C_{1-6} alkyl and C_{1-6} hydroxyalkyl; and,

each n is an integer from 0-4;

and wherein the compound of Formula I comprises at least two hydroxy groups.

In another aspect, the present disclosure provides a method for the preparation of a compound of Formula I as defined above comprising:

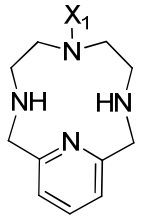
(i) activating the carboxylate groups of a compound of Formula II with a peptide reagent



(II); then,

(ii) coupling said activated compound of Formula II with an amine derivative of substituent $-NR^1R^2$ to arrive at said compound of Formula I wherein R^1 and R^2 are as defined herein.

In another aspect, the present disclosure provides a method for the preparation of a compound of Formula II as defined herein comprising alkylation of a compound of Formula III:



(III)

wherein X_1 is methyl or $–(CH_2)_3$-COOH.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound of Formula I as defined above together with a biocompatible carrier in a form suitable for mammalian administration.

In another aspect, the present disclosure provides a method comprising:

(i) administration to a subject of the compound of Formula I

as defined above or the pharmaceutical composition as defined above;

(ii) detection of magnetic resonance (MR) signals from said subject or parts of said subject in which said compound has distributed;

(iii) generation of MR images and/or MR spectra from said detected signals.

The compounds of the present disclosure have been demonstrated to possess properties that indicate their usefulness as MRI contrast agents.

The solubility of compounds of the disclosure measured as described in Example 13 demonstrated their suitability for use as contrast agents for MRI.

In vitro relaxivity measurements to evaluate the efficiency of compounds of the disclosure (see Example 14) demonstrated that these compounds induce an increase of both the longitudinal and transverse relaxation rates (e.g., $1/T_1$ and $1/T_2$ respectively) of the water molecules coordinated with the metal ion.

Experiments to test the kinetic inertness of compounds of the disclosure was evaluated in the presence of competing metal ions Cu^{2+} and Zn^{2+} in slightly acidic solution (see Example 15). These experiments demonstrated that compounds of the present disclosure have favourable characteristics compared with the prior art.

Compounds of the disclosure showed an improvement in the kinetic inertness of the Mn(II) based chelates with a slower dissociation compared to a prior art compound.

In summary therefore, the compounds of the present disclosure demonstrate an advantageous balance between contrast agent efficiency and improved stability *in vivo* not previously demonstrated Mn(II) chelate compounds. The additional *in vivo* stability indicates that the compounds of the disclosure could be an attractive alternative to Gd(III) in the future generation of clinical contrast agents for medical MRI.

Brief Description of the Figures

Figure 1 illustrates the dissociation kinetics of Mn(II) based chelates as tested