Iron paraCEST MRI Contrast Agents

Scientists from the University of Goettingen developed first row transition metal ions (i.e. Fe/ iron) supported by macrocyclic ligands to provide paraCEST based alternatives to lanthanide contrast agents - thus NOT using gadolinium. They are tripodal imidazole- or pyrazole-derivative, Schiff base ligands to provide water-soluble coordination complexes with i.e. iron, that act as paraCEST agents that will provide signal contrast in MRI.

Challenge

Magnetic resonance imaging (MRI) is a non-invasive in vivo diagnostic imaging technique utilizing non-ionizing radio frequency radiation. It requires the collection of a baseline scan and the use of contrast agents to obtain an image. The use of contrast agents in diagnostic medicine is rapidly growing. German market alone trespassed 90 Mio. Euro per year. Current contrast agents in clinical use are mainly based on lanthanides (like Gadolinium) supported by macrocyclic ligands. They have a number of deficiencies, i.e. (i) localized disturbances in osmality, which can lead to edema and other undesirable reactions, (ii) toxicity, due to the release of free metal ions from the complexes, (iii) they are expensive. There is a need for new and more effective agents requiring lower dosage use, lower toxicity, higher resolution and more organ/disease specificity.

An alternative is chemical exchange saturation transfer (CEST) imaging as a new MRI contrast approach in which exogenous or endogenous compounds containing either exchangeable protons or exchangeable molecules are selectively saturated and, after transfer of this saturation, detected indirectly through the water signal with enhanced sensitivity. CEST constitutes a powerful sensitivity enhancement mechanism in which low concentration solutes can be visualized through the water signal.

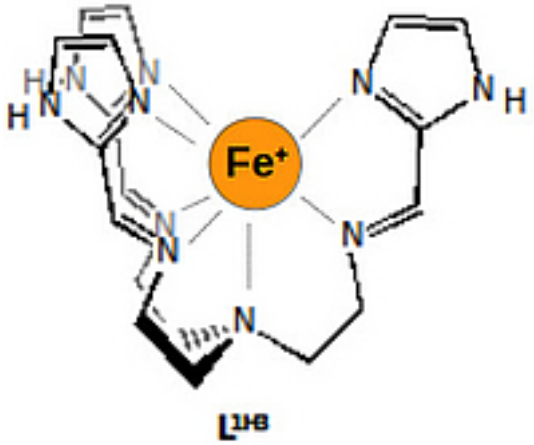
Our Solution

Scientists from the University of Goettingen developed first row transition metal ions (like i.e. iron, Fe) supported by macrocyclic ligands to provide alternatives to lanthanide-based paraCEST contrast agents. They are tripodal imidazole- or pyrazole-derivative, Schiff base ligands to provide water-soluble coordination complexes that act as paraCEST agents that will provide signal contrast in MRI.

This invention is relevant to the field of biological imaging, in particular Magnetic Resonance Imaging (MRI) in the clinical and veterinary setting. The invention derives from inorganic coordination chemistry, and is the first use of tripodal Schiff base ligands as defined in the claims to support first-row transition metals to provide water-soluble coordination complexes that act as paramagnetic chemical exchange saturation transfer (paraCEST) agents that will provide signal contrast in MRI.

Surprisingly, Z-spectra col
contrast as compared with
thus providing innovative p

with diseased tissue, i.e. ir



Advantages

- Use of transition metals (i.e. FE) avoids toxicity issues arising from the use of Ln III based agents (i.e. Gadolinium).
- Substituting economically and environmentally costly lanthanides/gadolinium with more abundant transition metals like iron, will have financial and environmental benefits.
- Ligands exhibit high kinetic stability under aerobic conditions in the dissolved state at physiologically relevant pH and ionic strength.
- The compounds are stable at increased temperatures and different pH-values.
- The compounds show excellent high paraCEST efficacy.
- ParaCEST allows versatility, exhibiting properties that allow for the sensing of temperature, pH, metabolites, metal ions, as well as proteins and enzymes.

Applications

Use for human diagnosis in clinics and for in vivo research.

Developmental Status

In the lab stage.

Patent Status

We filed international PCT-IP rights and are looking for a licensing partner interested in further developing and marketing this innovation.

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