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Bimodal nanoprobes based on non-covalent association of Gd(III) chelates and anionic or cationic quantum dots for optical and magnetic resonance imaging

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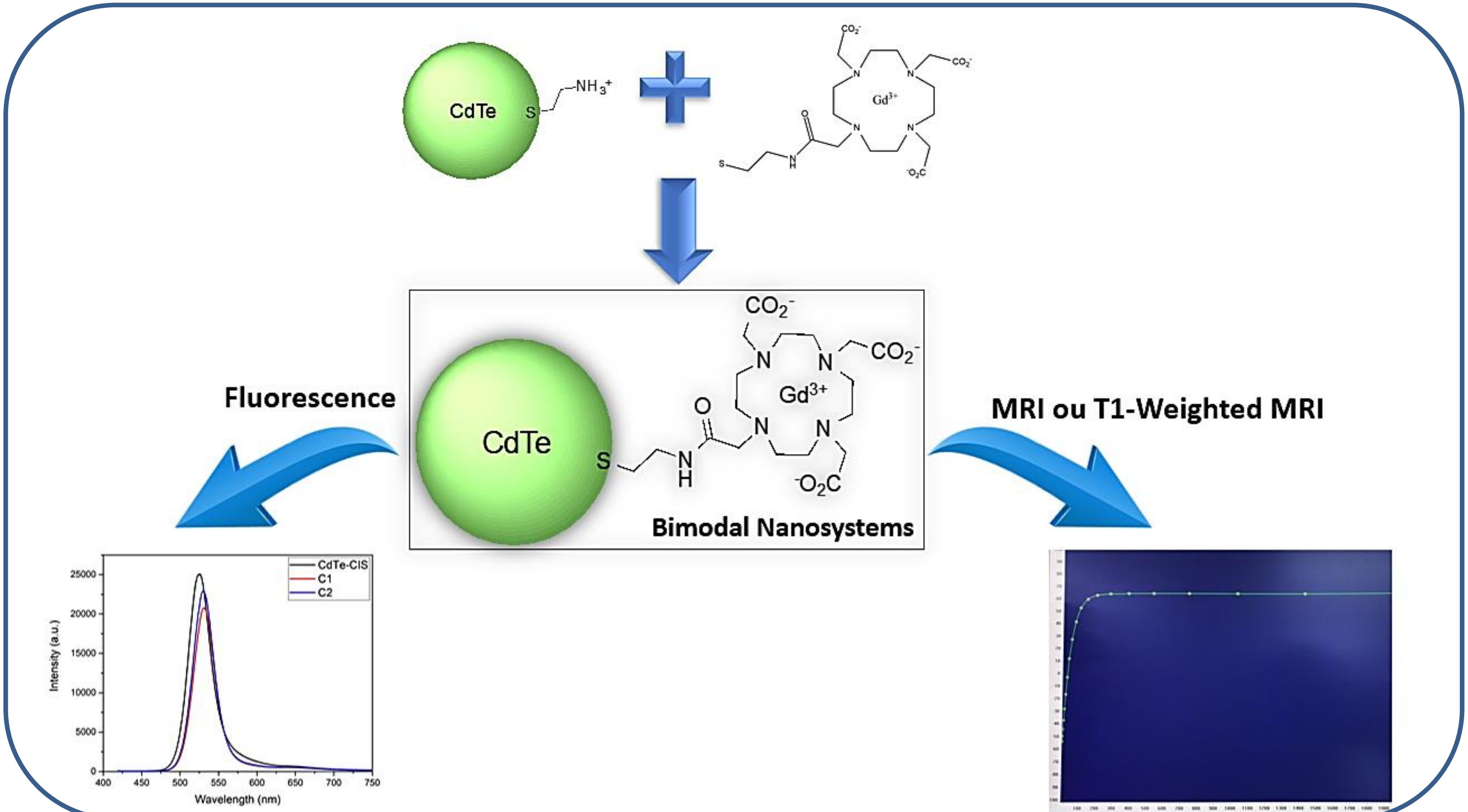

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Abstract

Magnetic resonance imaging (MRI) is one of the most applied imaging techniques in the clinical diagnostic field. Has several advantages over other techniques. However, the low sensitivity and insufficient contrast are significant drawbacks of this technique. To improve the image resolution, frequently are applied contrast agents (CAs), such as Gd(III) chelates. Several approaches have been reported to increase the efficiency of these CAs, and among them are nanoparticulate systems. Moreover, by associating MRI CAs with fluorescent nanoparticles, it is possible to obtain versatile dual nanoprobes. Quantum dots (QDs) are fluorescent nanocrystals, that have high photostability and chemically active surface.

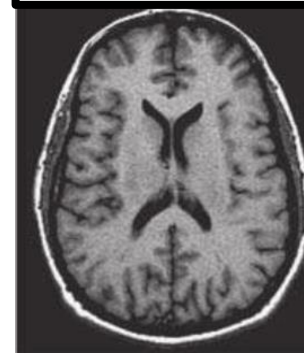
In this work, we developed bimodal nanosystems by associating CdTe QDs with Gd(III) chelates. Intending to compare the effect of the stabilizing functional groups in the CAs relaxivity, we used carboxylated and amine-coated QDs. The Gd(III) chelates, modified with a thiol group, were attached to the QDs surface, affording the bimodal systems. Our preliminary results showed that the stabilizing agent influences the relaxivity values of these bimodal nanoprobes. Nevertheless, the optical and relaxometric characterizations showed that these nanoprobes have potential to be used as CAs for optical and MR imaging.

Keywords: Quantum Dots, bimodal system, magnetic resonance imaging

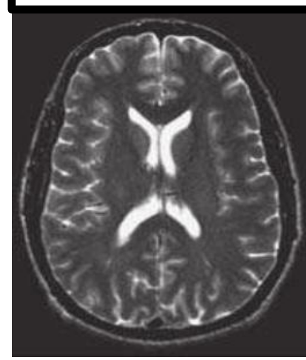
Magnetic Resonance Imaging (MRI)

- **Main diagnostics techniques**
- **Differentiate healthy and pathological tissues**
- **Good spatial resolution**
  - → **Low sensitivity**
- **Contrast Agents (CAs)**

***T_1* images**

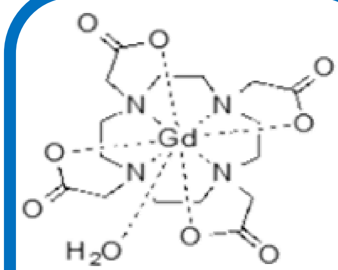


***T_2* images**

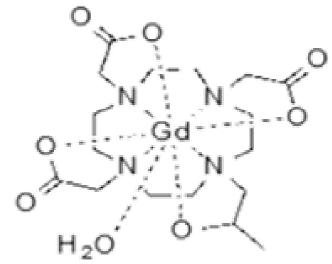


Chelates of Gd^{3+}: most used Contrast Agents

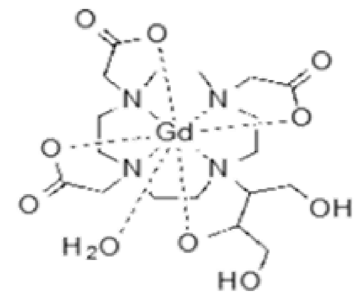
Macrocyclic chelates of Gd^{3+}



Dotarem®
DOTA-Gd
r_1 = 4.2 $mM^{-1}s^{-1}$

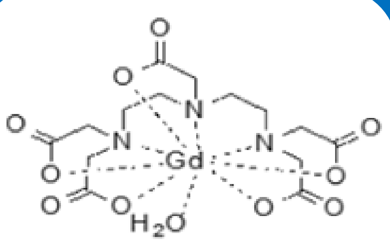


Prohance®
(HP-DO3A)-Gd
r_1 = 4.4 $mM^{-1}s^{-1}$

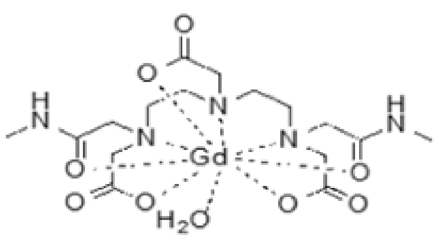


Gadovist®
(DO3A-butrol)-Gd
r_1 = 5.3 $mM^{-1}s^{-1}$

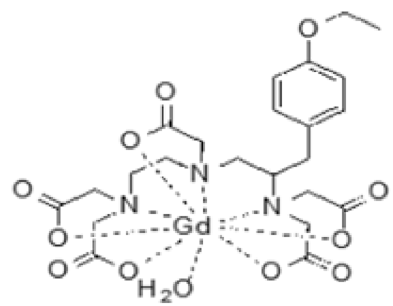
Linear chelates of Gd^{3+}



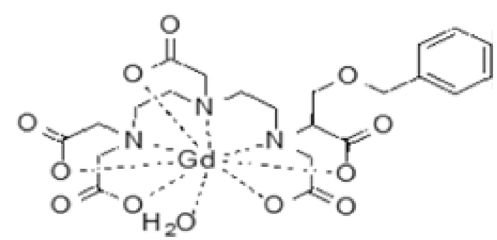
Magnevist®
DTPA-Gd
r_1 = 4.3 $mM^{-1}s^{-1}$



Omniscan®
(DTPA-BMA)-Gd
r_1 = 4.6 $mM^{-1}s^{-1}$



Multihance®
BOPTA-Gd
r_1 = 6.7 $mM^{-1}s^{-1}$



Eovist®
(EOB-DTPA)-Gd
r_1 = 7.3 $mM^{-1}s^{-1}$

Magnetic Resonance Imaging (MRI)

- Low sensitivity → μM concentration

→ CAs aren't sufficient

↓

High contrast observed

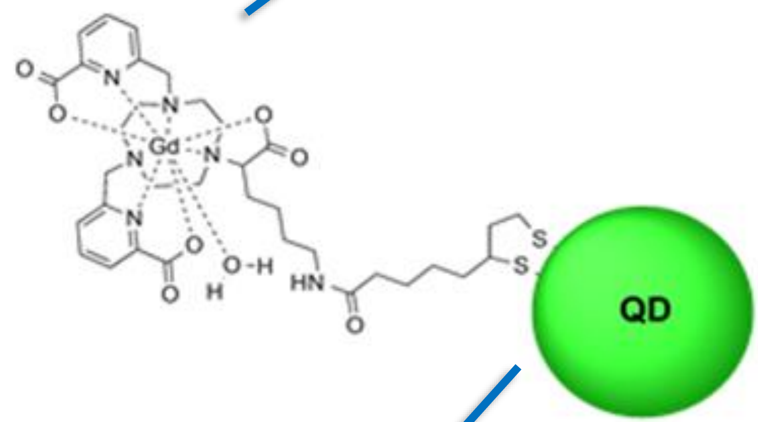
↑ local [CAs] ⇒ ↑ dosage of CAs

Nanotechnology and MRI

Nanoparticulate contrast agents

Bimodal systems

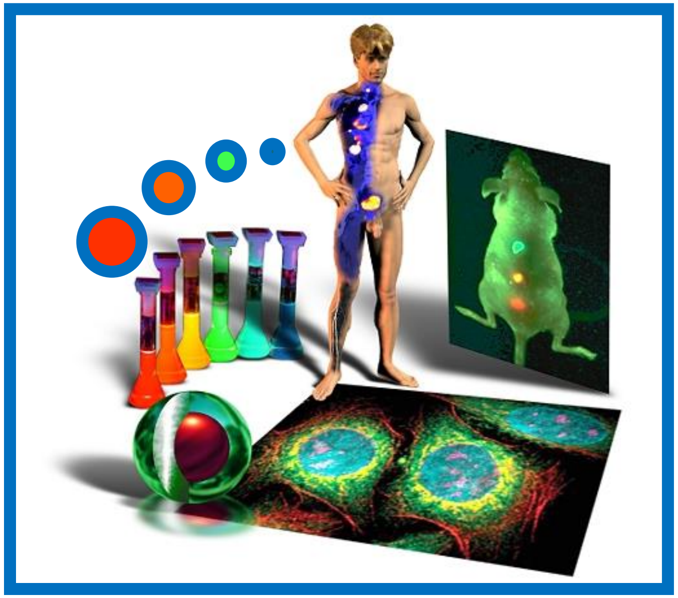
Paramagnetic

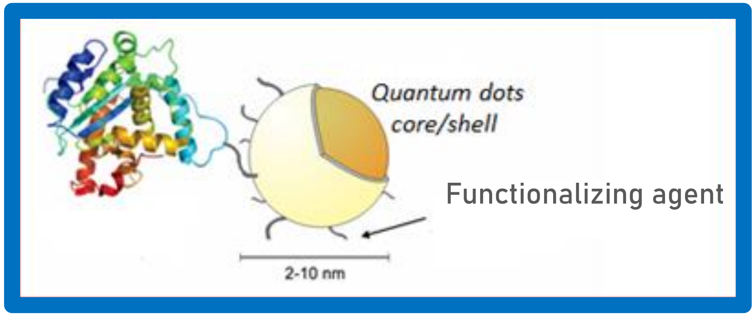


Fluorescent

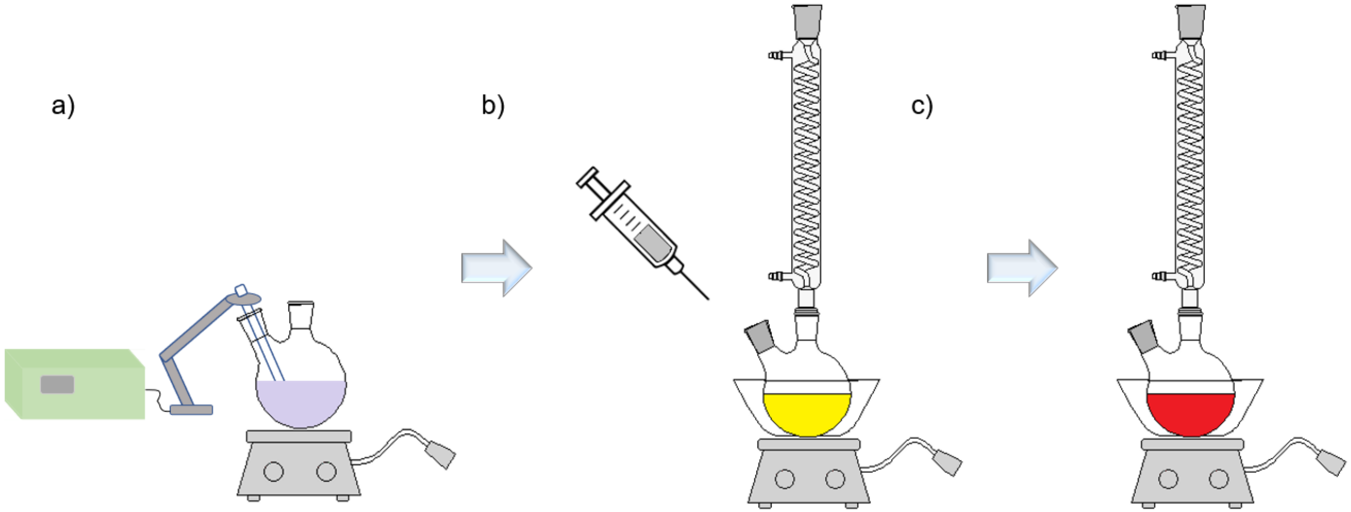
Quantum Dots (QDs)

- **Fluorescent;**
- **Resistance to photodegradation;**
- **Highest number of gadolinium (Gd^{3+}) chelates;**
- **Active surface.**



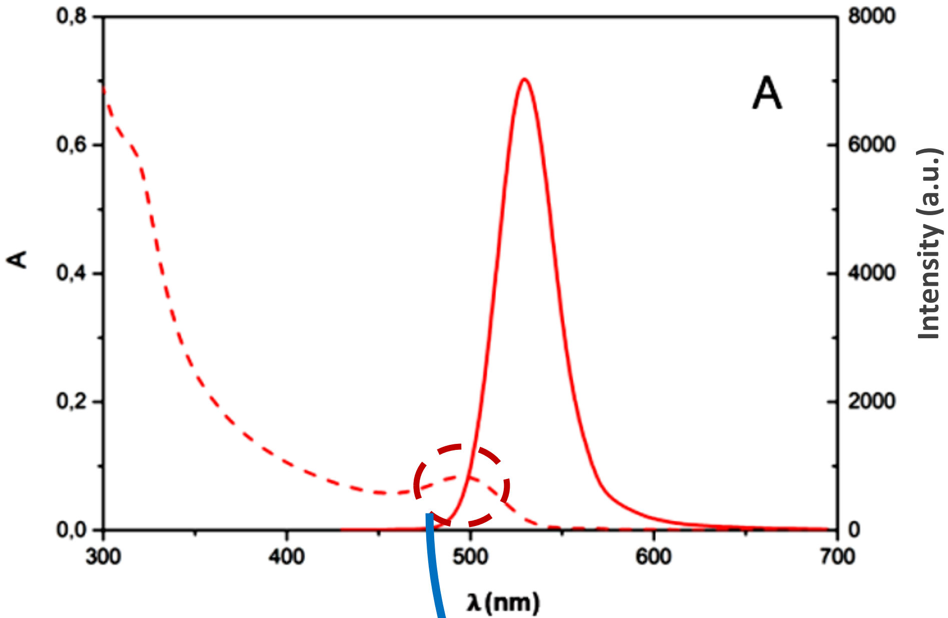


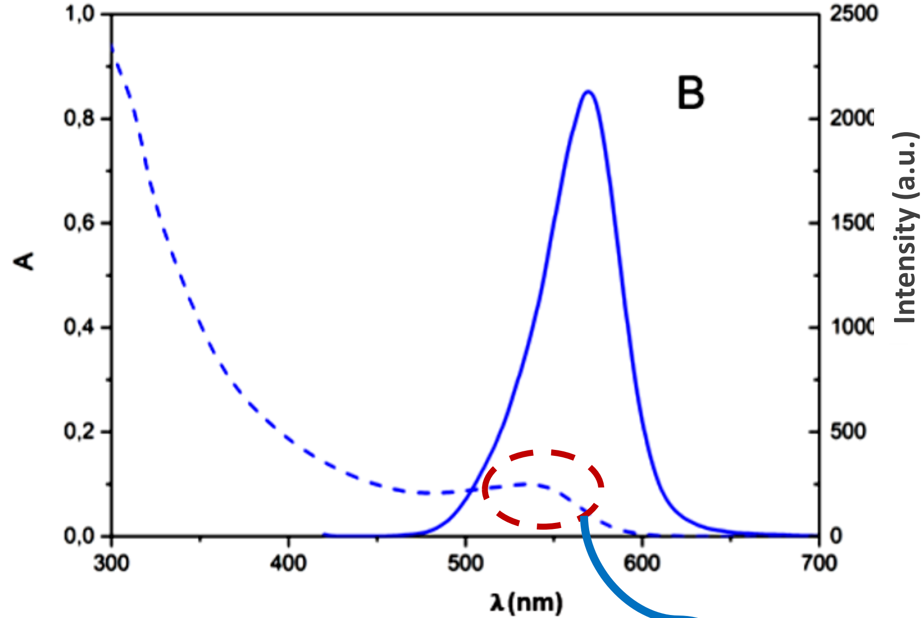
Synthesis of QDs



Stabilizer	pH	Proportion Cd:Te:stabilizer
CIS	5.8	10:1:12
MSA	10.5	2:1:2.4

Optical characterization of QDs





CdTe-CIS

d = 2.65 nm

[CdTe-CIS] = 10.42 μM

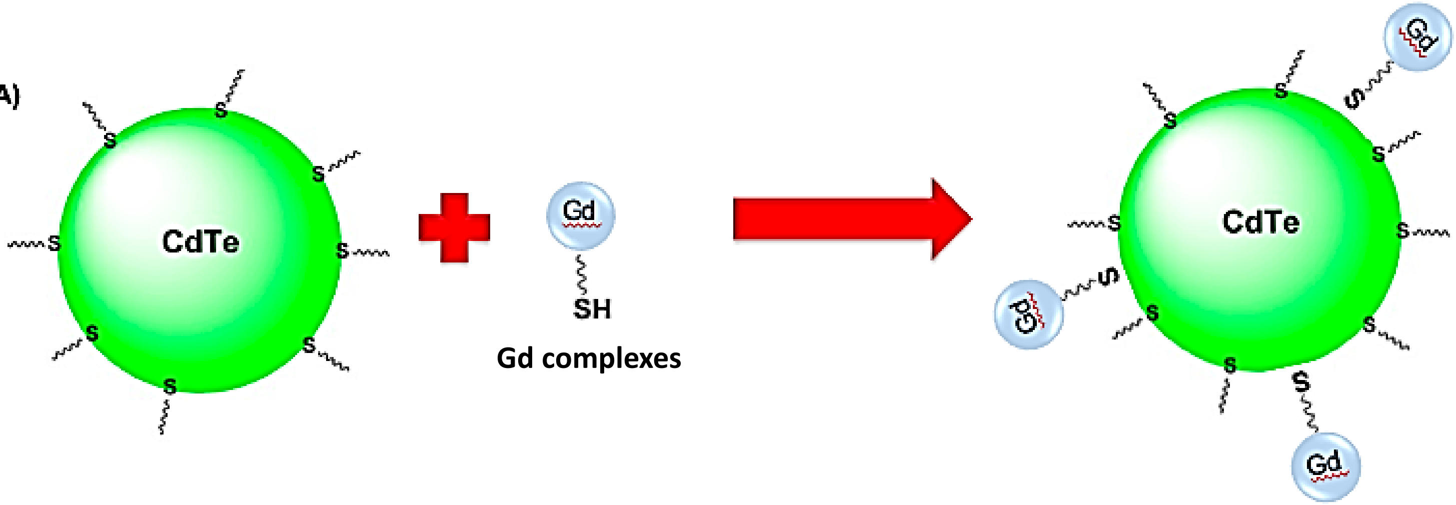
CdTe-MSA

d = 2.90 nm

[CdTe-MSA] = 6.56 μM

Preparation of Bimodal Systems

(A)

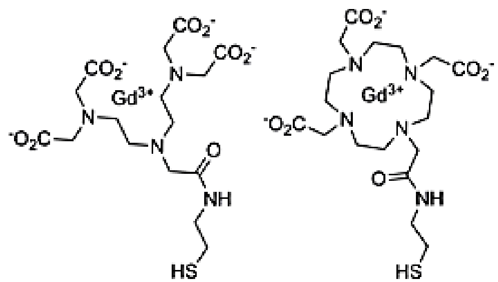


(B) Stabilizer

Cysteamine (C)

Mercaptosuccinic acid (M)

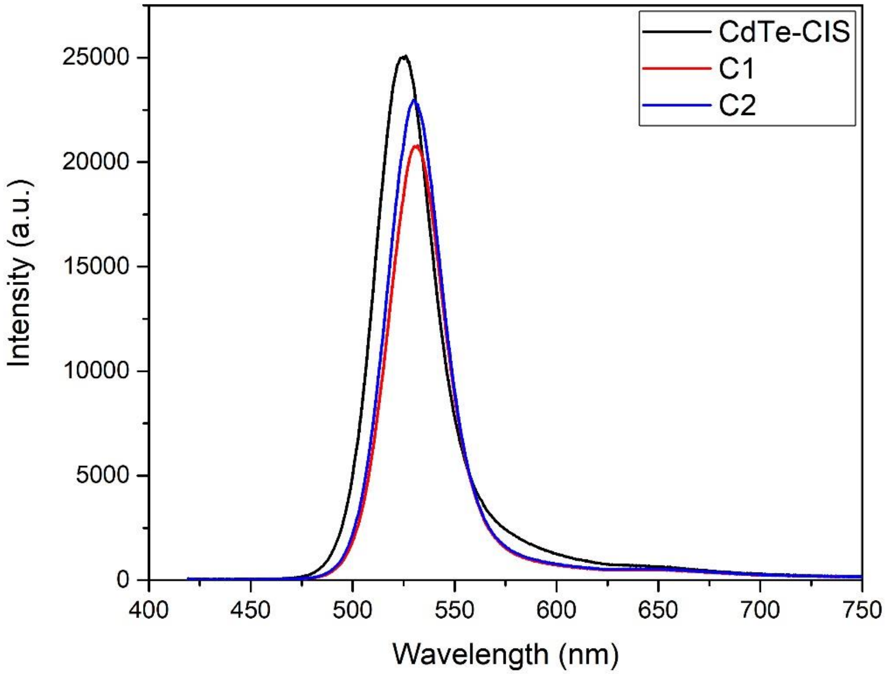
(C) Complexes

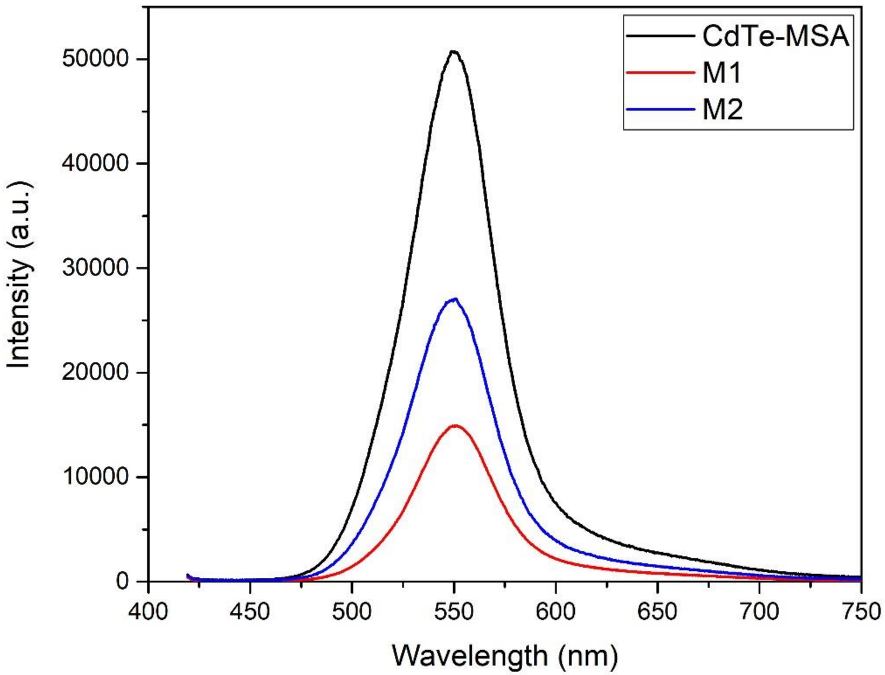


DTPA-Cis (1)

DOTA-Cis (2)

Emission optical characterization





Relaxometric characterization

System	T_1	r_1 (mM^{-1}s^{-1}) *per* Gd (III) Nominal	r_1 (mM^{-1}s^{-1}) *per* Gd (III) Real	r_1 (mM^{-1}s^{-1}) *per* QD Real
CdTe-CIS	3240	-	-	-
C1R	1750	3.7	6.2	25.1
C2R	2400	1.5	3.3	10.3
CdTe-MSA	3370	-	-	-
M1R	1368	10.8	16.1	66.2
M2R	2740	1.7	4.0	10.4

DTPA-Gd

4.3 mM^{-1}S^{-1}

DOTA-Gd

3.6 mM^{-1}S^{-1}

Conclusion

- Bimodal systems were developed associating anionic and cationic CdTe QDs to Gd complexes by non-covalent conjugation;
- The conjugation methodology used is promising, in addition to being a versatile and easy to execute method;
- The optical and relaxometric studies carried out showed that the prepared bimodal systems present themselves as promising bimodal CAs for biological studies by fluorescence and MRI.

Acknowledgments

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