Effect of Quinoline Amide Substituents on the Luminescence and Magnetic Resonance Imaging (MRI) Properties of Bimodal Europium (III) Complexes

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Introduction

- Surgical intervention is often used in the management of cancers.[1]
  - Discrimination between malignant and healthy tissue is a major obstacle that can lead to insufficient tumor resection.[1]
- Use of a dual-modality imaging agent with both magnetic resonance imaging (MRI) and Optical Imaging properties could potentially improve tumor visualization before and during surgery (**Figure 1**).[2,3]

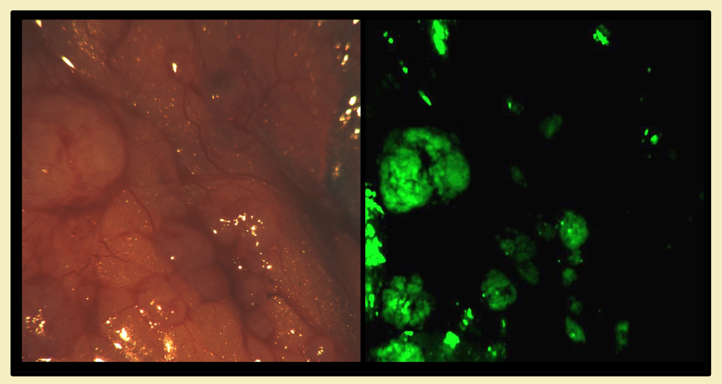


Figure 1. View of localized cancerous region with the naked eye (left) and with the aid of a tumor-targeted fluorescent dye (right).[3]

- Lanthanide ions such as Europium possess long-lived luminescence lifetimes, making them ideal candidates for bimodal imaging probes.
  - To obtain high-resolution images, however, high energy laser excitation is required, which can be damaging to biological tissue.

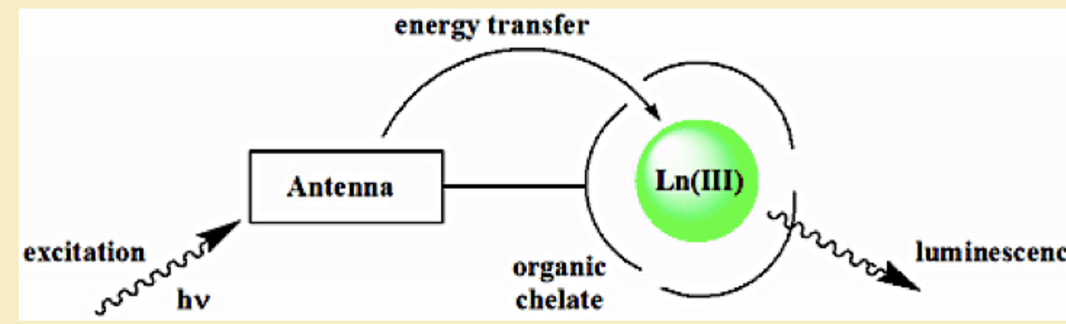


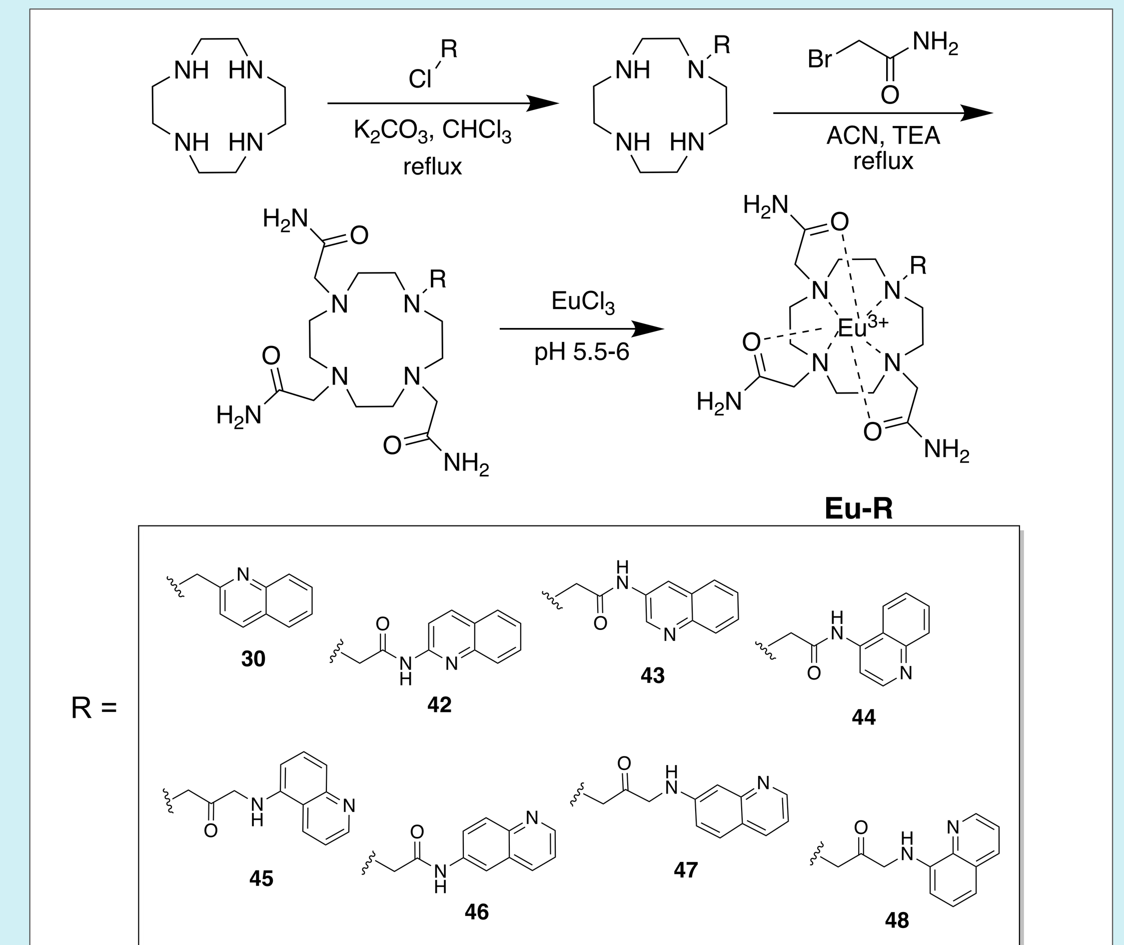
Figure 2. Visual diagram of the antenna effect.[4]

- To overcome this limitation, an organic chromophore can be used as an "antenna" to sensitize the luminescence of the lanthanide ion upon excitation from a lower energy light source.
- The efficiency of this sensitization process is influenced by the nature of, and the distance from the lanthanide ion.

Project Goal

- The goal of this project is to synthesize a library of Europium (III) complexes and determine which has optimal luminescence and MRI properties.
- Our hypothesis is that the variation among the quinoline antennas will alter the optical imaging properties, which will be reflected in the luminescence intensities of the complexes.

Methods and Materials



Scheme 1. Synthetic scheme for Eu^{3+} complex library

Reagents and Materials

All reagents and solvents were purchased from commercial vendors and used as received.

Ligand Synthesis

Ligands were synthesized according to **Scheme 1**. Cyclen was monoalkylated with the appropriate quinoline sidearm and purified by pH extractions. The resulting products were reacted with 2-bromoacetamide and isolated from the reaction mixture by filtration. All ligand identities were verified by ^{1}H and ^{13}C NMR spectroscopy.

Metal Complexation

Europium complexes were prepared by mixing equimolar amounts of $EuCl_3$ and ligand at pH 5.5-6. The absence of excess metal in solution was confirmed with a Xylenol Orange Test.

Results and Discussion

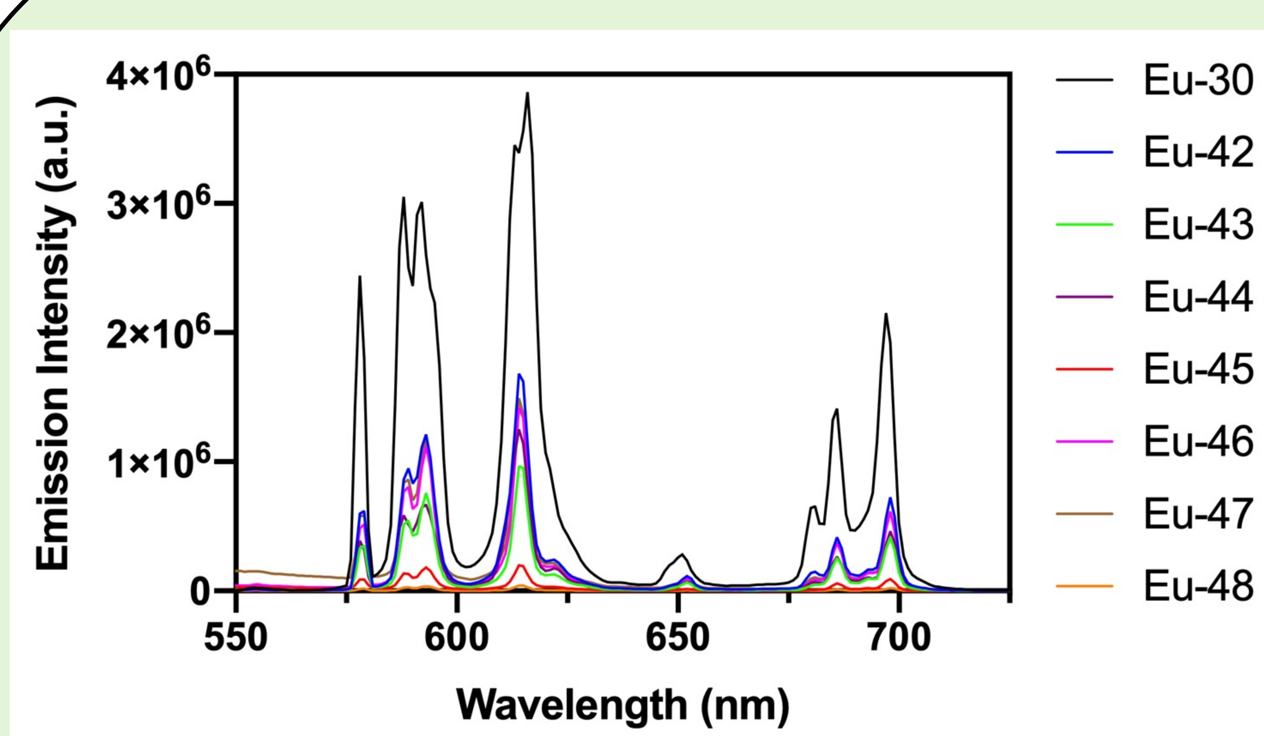


Figure 3. Emission spectra of 1E-4 M Eu^{3+} complexes in 0.1 M HEPES buffer (pH 7.4). Emission spectra were acquired upon excitation at wavelengths specific to each complex.

Evaluation of Spectroscopic Properties

- The emission spectra shown in **Figure 3** demonstrates luminescence sensitization via the quinoline antenna.
  - The differences in intensities can be attributed to the differences in coordination sites and amide substituent location.
- The luminescence intensities are far greater when the quinoline is excited in comparison to direct excitation of the metal ion (**Figure 4**).
  - This indicates that the quinoline is effectively sensitizing the luminescence of the lanthanide ions.
- Eu-30 exhibits the highest emission intensity due to the direct coordination (shorter distance) of the quinoline antenna with the Eu^{3+} ion.
- Eu-45 and Eu-48 exhibit the lowest emission intensities.

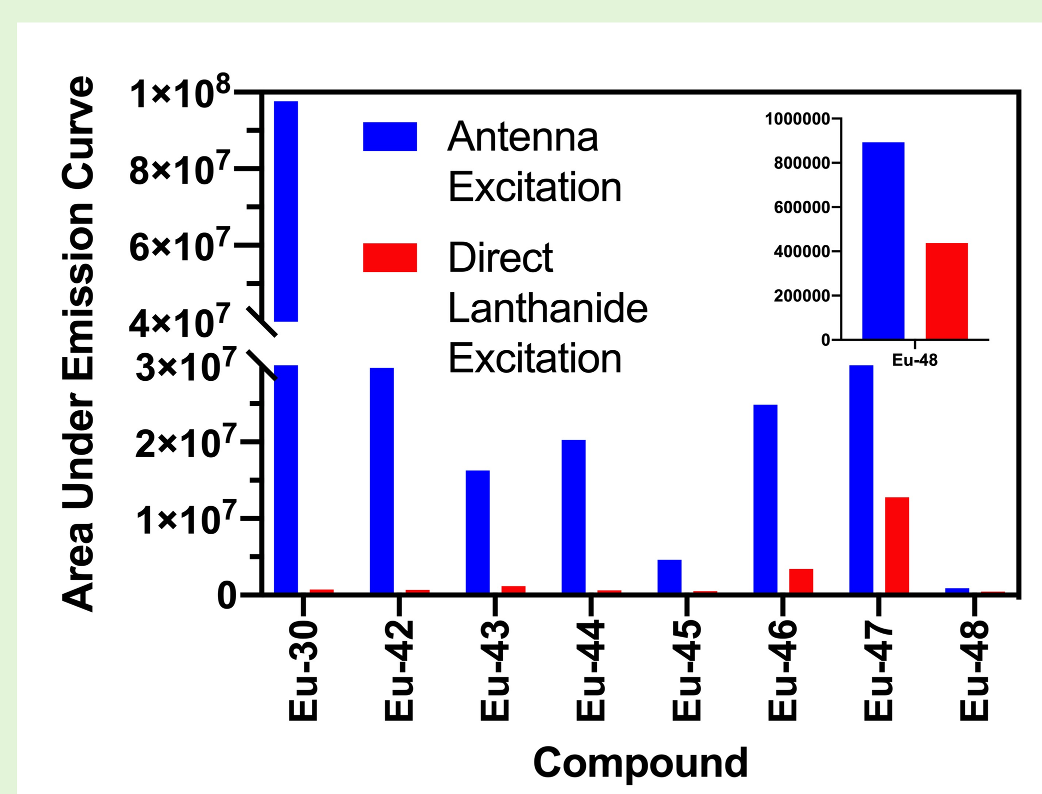


Figure 4. Comparison of the area under the emission curve for each complex upon antenna excitation (blue) and direct lanthanide excitation (red).

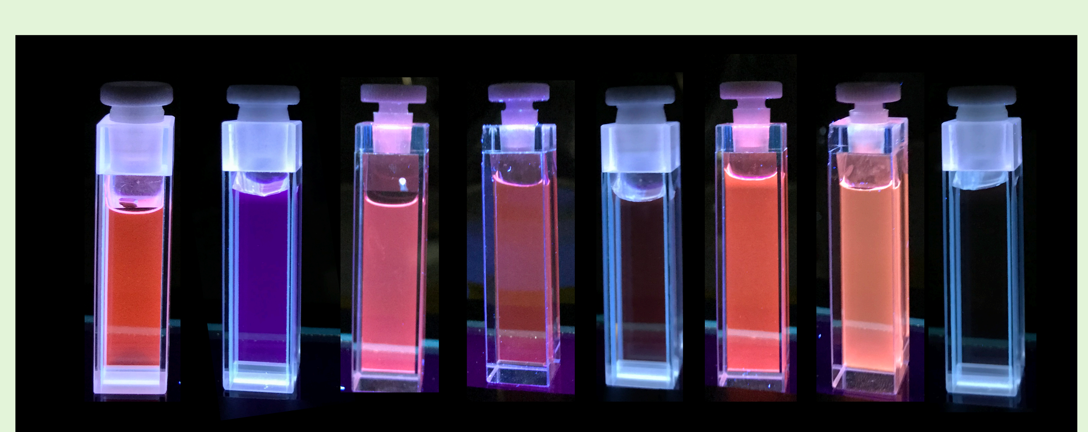


Figure 5. From left to right, Eu-30, Eu-42, Eu-43, Eu-44, Eu-45, Eu-46, Eu-47, and Eu-48 (1E-4 M) in 0.1 M MES buffer (pH 7.5). All compounds were excited using a UV light source at 302 nm except Eu-44 that was excited at 365 nm.

- All compounds display red light characteristic of Eu^{3+} complexes with varied intensities (**Figure 5**).

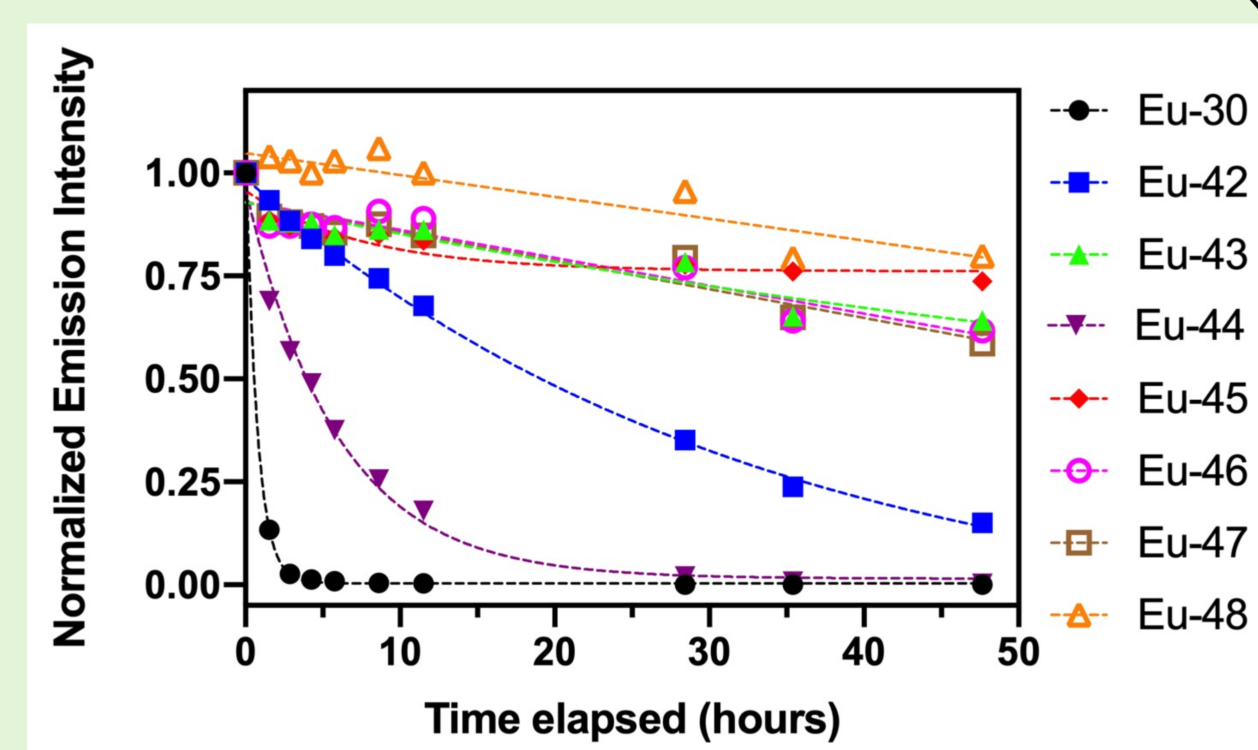


Figure 6. Normalized emission intensities of Eu^{3+} complexes following incubation in citrate buffer (10 mM, pH 3) over 48 hours at 310 K. Dashed lines represent mono-exponential decay fits of the data.

Measurement of Stability

- For lanthanide complexes to be useful *in vivo*, they must demonstrate stability at physiological conditions to ensure that free metals are not released in the body.
- For a complex with poor kinetic stability, the metal ion would easily dissociate from its ligand. This would increase the distance between the metal and the antenna and result in a reduction in emission intensity.
- Although Eu-30, Eu-42, and Eu-44 exhibit adequate luminescence intensities (**Figures 3,4**), they exhibit the lowest kinetic stabilities (**Figure 6**).
- Eu-43, Eu-46, and Eu-47 appear to be more stable than the other complexes while also demonstrating acceptable luminescence capabilities. These compounds appear to be more promising candidates for future experimentation.

Conclusion

- Amide substituent location affects optical imaging properties.
- Eu-30 has the highest emission intensity but is the least stable compound while Eu-48 has the lowest emission but is the most stable. Due to this, both compounds are not ideal candidates for dual modality imaging agents.
- Compounds Eu-43, Eu-46, and Eu-47 possess the highest level of stability and emission intensity. These complexes show the most promise for further study.

Future Work

- Evaluate the NMR and PARACEST MRI properties of the library of complexes.

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