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22

A NOVEL TETRAVALENT AND POLYDENTATE MULTIFUNCTIONAL LIGAND WITH POTENTIAL FOR GALLIUM-67 UPTAKE: SYNTHESIS AND CHARACTERIZATION

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Introduction/Justification

Nuclear medicine utilizes gallium radioisotopes as key components in theranostics, integrating diagnostic imaging and therapy. However, clinical translation faces the challenge of the instability of the free gallium ion. By chemically mimicking iron, gallium can interact with proteins such as transferrin, which reduces diagnostic specificity and increases the risk of adverse effects. Thus, the development of high-affinity chelating agents is necessary. The use of a tetravalent and hexadentate ligand is strategic, as it completely fills the metal's coordination sphere, ensuring the stability necessary to prevent ligand exchange. This approach is fundamental to overcoming barriers from basic research to clinical application, ensuring more precise and safe diagnostic agents in oncological management.

Objectives

To synthesize a novel tetravalent and polydentate multifunctional chelating agent H4L, perform its complexation with gallium(III) for structural characterization, and establish the basis for future radiolabeling studies with gallium-67.

Materials and methods

The H4L ligand was synthesized by a reductive amination followed by an alkylation reaction with 2-hydroxy-3-chloromethyl-5-methylbenzaldehyde, which was prepared by a 3-step organic synthesis, following a well-established methodology already established in the group. The precursor is synthesized via Schiff base reaction between salicylaldehyde and ethylenediamine, under reflux for 15 minutes in ethanol. After this reaction, the imine was reduced using NaBH4 in ethanol under stirring for 10 minutes, and then, after purification, the amine was alkylated in a reaction at 50°C for 48 hours in acetonitrile/dichloromethane. The ligand H4L was obtained as a yellow solid. The gallium complex, named [Ga(HL)], was synthesized by reacting the H4L ligand with gallium chloride in acetonitrile under overnight reflux, resulting in a yellow solid.

Results

The H4L ligand was obtained in ca. 80% yield and the [Ga(HL)] complex in 65% yield. The ligand's formation was confirmed by several techniques, including infrared and UV-vis spectroscopies, NMR (1H, 13C, HSQC, and HMBC), and mass spectrometry, and the expected isotopic pattern was observed. Preliminary analysis of the gallium complex [Ga(HL)] indicated its formation, with the coordination of the metal to the ligand observed in infrared spectroscopy. Further analyses will be performed to confirm the formation and geometry of the complex.

Conclusion

The H4L ligand was successfully synthesized with high relative purity. The formation of the gallium complex demonstrates the potential of this chelating agent to stabilize the metal in a favorable geometry. This project represents an advance in the search for versatile molecular platforms, allowing future bioconjugation to obtain a radiopharmaceutical with high specificity. The next steps include optimizing the synthesis of the complex and radiolabeling studies with 67Ga (C2TN/Portugal), aiming at validating this new tool as a possible diagnostic agent.

Previous Next

Keywords

Polydentate ligand; Gallium-67; Radiopharmaceutical; Diagnostic agent

Conflicts of interest: Not declared.

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