

**Título:** DISEÑO Y SÍNTESIS DE COMPUESTOS DE COORDINACIÓN CON AFINIDAD POR ACÚMULOS DE B-AMILOIDE

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**Resumen:** Our initial hypothesis is that, coordination compounds containing the fragment  $^{99m}\text{Tc}$  and fragments with affinity to  $\beta$ -amyloid ( $\text{A}\beta$ ), could be used in the diagnosis of Alzheimer's disease (AD). The early diagnosis of this disease is important as it is one of the most common dementias affecting a large number of the older population. We choose that the coordination complexes possess  $\text{A}\beta$  related compounds by incorporating groups as benzothiazole, stilbene, benzoxazole or azobenzene, because it is known that accumulations of this peptide are present in the brains of patients affected by the AD. On the other hand, we chose the  $^{99m}\text{Tc}$  fragment because it is the most commonly used radionuclide in SPECT (Single-photon emission computed tomography) which is widely available in nuclear medicine centers. Its main advantage over other imaging techniques such as X-rays, ultrasound or magnetic resonance, is its unlimited depth of penetration.

In addition, the rhenium complexes are usually used as model compounds of the corresponding  $^{99m}\text{Tc}$  derivatives in the early phases of the design of radiopharmaceuticals based on this metal. For these reasons, we have focused primarily on the design and synthesis of rhenium(I) coordination compounds and then we have realized the study of the behavior of some of these ligands against technetium(I) to verify their coordinative similarity.

In the present work we described the design and the synthesis of ligands acting as bidentate

(thiosemicarbazones H2L1-12 and pyridine derivatives: hydrazones L13-15, imine derivatives L16-18 and amines derivatives HL19-21) and ligands acting as tridentate (thiosemicarbazones HL22-29 and thiocarbonohydrazones HL30-31) which give very stable complexes with the metal centers Re(I)/Tc(I). All the compounds were characterized by elemental analysis, mass spectroscopy, spectroscopic methods such as NMR, IR or UV-vis and the crystal structure analysis for a large number of these compounds.

The reaction of the thiosemicarbazone ligands (H2L1-12) with different rhenium precursors ( $[\text{ReX}(\text{CO})_5]$  and  $[\text{ReX}(\text{CO})_3(\text{CH}_3\text{CN})_2]$ , X=Cl or Br) in different reaction conditions yielded new complexes of general formula  $[\text{ReX}(\text{CO})_3(\text{H2L})]$  (1-12a X=Cl or 1-12b X=Br). Spectroscopic data and the single crystal diffraction studies confirmed the formation of five-membered chelate rings via coordination of the sulphur and hidrazinic nitrogen atoms. It has also been possible to obtain complexes of general formula  $[\text{Re}_2(\text{CO})_6(\text{HL})_2]$  (1-12c) in which the ligands are deprotonated and the sulphur atoms bridge two rhenium atoms. Moreover in the case of H2L3, it was possible to obtain the structure of a tetrameric complex with the formula  $[\text{Re}_4(\text{L3})_2(\text{CO})_{12}(\text{EtOH})_2]$  (3d), where the ligands are bideprotonated and the four metal centers have an octahedral geometry, although two types of metal centers with different coordination environment can be observed.

The reaction of nine pyridine derivatives ligands (L13-18 and HL19-21) yields eighteen adducts with similar formula to thiosemicarbazone derivatives (13-21a X=Cl or 13-21b X=Br). Spectroscopic data and the X-ray studies show that these compounds are coordinated to the metal by the pyridinic (N1) and hydrazinic, imine or amine (N2) nitrogen atoms, giving a five-membered chelate ring. This coordination involves changes in the orientation of pyridine ring. Moreover, we have been able to observe the presence of two different conformers in different solvents, by means of the NMR study and X-ray diffraction in the case of complex 20a. In addition, the amine derivatives are converted into their corresponding imine derivatives when their solutions in DMSO or DMF are stored at room temperature. This reaction was followed by NMR, UV-Vis and X-ray diffraction.

The reaction of the adduct  $[\text{ReX}(\text{CO})_3(\text{CH}_3\text{CN})_2]$  (X=Cl,Br) with thiosemicarbazones and thiocarbonohydrazones derived from pyridine (HL22-31) allowed the isolation of compounds of general formula  $[\text{Re}(\text{L22-31})(\text{CO})_3]$  (22-31e) where the ligand is tridentate. The isolation process was sometimes difficult due to the tendency of these compounds to form colloidal aggregates, which could be characterized by transmission electron microscopy (TEM). Single crystal diffraction studies confirm the formation of two five-membered chelate rings via coordination of the pyridine (N1) and imine (N2) nitrogen atoms and the sulphur atom (S1).

The studies with the Tc(I) cation are centered on the reactivity against to thiosemicarbazone ligands (H2L1, H2L2 and HL27). The spectroscopic studies (IR) show that the isolated complexes are similar to the rhenium derivatives.

Finally, studies of affinity for  $\beta$ -amyloid accumulations of the more stable complexes and their corresponding ligands have been realized. For this, a reproducible method for preparation of the A $\beta$  fibers, providing fibers homogeneously, was designed. The fibers were characterized by TEM and AFM. Then, a first screening was performed, where it was verified that the complexes with the tridentate ligands gave better results of affinity. By means of competitive assays with thioflavine, the IC<sub>50</sub> values could be obtained and from them we were able to calculate values of K<sub>i</sub> for these compounds. The found values were comparable to those in the literature for similar compounds.

