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SYNTHESIS AND CHARACTERIZATION OF A NEW DIAMINODIOXIME, A POTENTIAL LIGAND FOR ^{99m}Tc RADIOPHARMACEUTICALS

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Abstract
This paper reports synthesis of a new diaminodioxime ligand, derivative of hexamethylpropyleneamine oxime (HM-PAO). The ^{99m}Tc(V)-d,l-HM-PAO complex is well-known radiopharmaceutical for regional blood flow imaging. The structure of the new ligand was investigated by elemental analysis, IR, ^{1}H and ^{13}C NMR. Complexation studies with ^{99m}Tc were carried out using stannous chloride as the reducing agent. The complex was characterized by paper chromatography and thin-layer chromatography. It was obtained in high yield when the reactions were carried out at pH=9. Also, it was found that the complex was stable up to 4 h.

Introduction
The radiopharmaceuticals currently being used for brain-perfusion studies are the ^{99m}Tc complexes of the tetradentate ligands hexamethylpropyleneamine oxime (HM-PAO) and ethylcysteinate dimer (ECD). Both the ligands form neutral and lipophilic complexes with ^{99m}Tc possessing an oxotechnetium core. While ^{99m}Tc-HM-PAO possesses two amine and two oxime donors, the ^{99m}Tc-ECD consist of two amine and two thiol donors [1]. The aim was to obtain the ligand which combines the best overall features of high brain uptake, fixed regional distribution within the brain and ease of radiopharmaceutical preparations [2]. The goal of this work was to examine the use of a new ligand as a potential candidate for the brain-perfusion imaging in single-photon emission computerized tomography (SPECT). The new ligand shows stereoisomerism, but we now report only preliminary research without the diastereo-enantio separation of isomeric mixtures of the meso- and d,l- diastereoisomers. This will be a part of further investigations.

Results and Discussion
Materials and methods: All reagents and solvents used in these studies were obtained from commercial sources without further purification. The $^{99m}TcO_4^-$ was

obtained from $^{99}Mo/^{99m}Tc$ generator prepared in our laboratory ("Vinča" Institute) and commercially available. IR Spectra were recorded on a Bomem MB 100 FTIR spectrophotometer in the form of KBr pellets. The ^{1}H and ^{13}C NMR spectral measurements were performed on a Varian Gemini 2000 (200 MHz). The spectra were recorded at room temperature in deuterated dimethyl sulfoxide (DMSO-d_6). Elemental (C, H, N) analysis of the samples was carried out by standard micromethods in the Center for Instrumental Analysis, Faculty of Chemistry, Belgrade. Radioactivity measurements of chromatography were performed in a NaI(TI) well-type gamma counter.

Preparation of ligand: 4,9-Diaza-3,10-diethylundecadiene-2,11-dione bis-oxime (LH_2) was prepared using the method described in the literature [3], with a slight modification, which included crystallization of the imine in petroleum-ether.

Preparation of ^{99m}Tc complex: Complexation studies of the ligand with ^{99m}Tc were carried out using stannous chloride as the reducing agent. 1 mg of ligand LH_2 was dissolved in 2.5 ml of water adjusted to pH 1.5-2 with concentrated HCl. Then, 13.5 μl of stannous chloride (5 mg dissolved in 0.05 ml of concentrated HCl and 4.95 ml of distilled water) was added and pH was adjusted to 9. 1.5 ml of sodium pertechnetate ($^{99m}TcO_4^-$, 0.5 mCi/ml) was injected into the vial. The vial was shaken for 1 min. The total reaction volume in vial was maintained at 4 ml.

Paper chromatography and thin-layer chromatography: The labeling yield was determined using a combination of two chromatographic systems: paper chromatography on Whatman No.1 with acetonitrile:water (1:1) as the mobile phase and TLC on silica gel 60 strips with saline as the mobile phase.

All the protons and carbon atoms for LH_2 (Table 1) were found to be in their expected regions, in accordance to IR spectroscopic and elemental analysis data (Table 2).

Table 1. ^{1}H NMR and ^{13}C NMR spectral data (δ ppm) for the ligand LH_2.

LH_2*	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)
^{1}H NMR	1.34 t	2.90 t	3.36 t	1.48 q	0.75 t	-	1.61 s	10.3 s	inv
^{13}C NMR	27.70	47.09	63.43	25.81	8.40	157.7	10.90	-	-

s, singlet; t, triplet; q, quintet, inv, invisible

***** structure of LH_2 with all the protons and carbon atoms is presented in the **Fig. 1**.

Table 2. Physical properties, elemental analysis and some vibrational frequencies for the ligand LH_2.

Comp.	m.p. (C°)	Yield (%)	Color	Calcd. (found)%			ν (-OH)	ν (-OH, NH)
				C	H	N		
LH_2	167	55	white	58.71	10.56	19.56	3257	3190
				(58.39)	(10.56)	(19.35)		

According to the literature data for similar diaminodioxime ligands and their ^{99m}Tc-labelled complexes [4], proposed structures of LH_2 and ^{99m}Tc-LH_2 are shown in Fig.1.

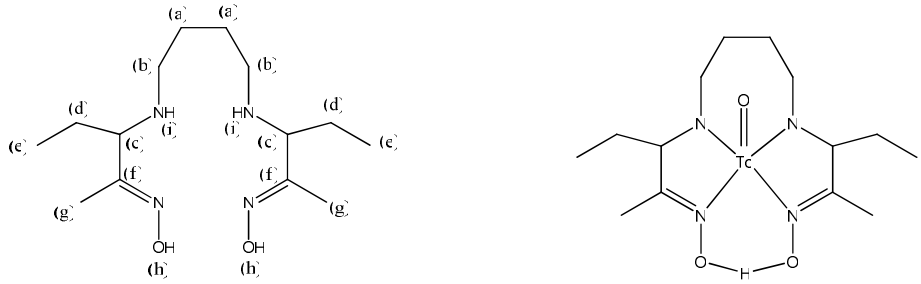

Fig. 1. Structure of LH_2 and proposed structure of ^{99m}Tc complex.

Radiochemical purity of the complex estimated at different time intervals are presented in Fig.2. Complexation reaction were done at pH=9.

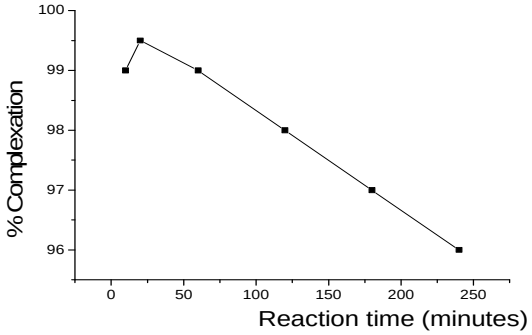

Fig. 2. Radiochemical purity of the complex.

Conclusion

A new tetradentate diaminedioxime ligand (LH_2) was successfully synthesized and characterized by elemental analysis, IR, ^{1}H, and ^{13}C NMR. From the obtained results, it can be concluded that ^{99m}Tc complex could be made easy with a ligand such as LH_2. This complex was obtained in good yield (> 95%) and was found to be stable in investigated conditions up to 4 h.

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