NEW SNS/S AND SNN/S MIXED LIGAND OXORHENIUM AND
OXOTECHNETIUM COMPLEXES CARRYING A PENDANT NITRO
GROUP ON THE MONOTHIOLOATE MOIETY AS HYPOXIA TISSUE
IMAGING

Jaipetch T.*, Pirmettis I., Papadopoulos M., Nock B., Main T.,
Raptopoulou C.P., Terzis A., and Chiotellis E.

* Section of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol
University, Bangkok 10700, Thailand.
Radiopharmaceutical Lab, Institute of Radioisotopes and Radiodiagnostic Products, NCSR " Demokritos ", Ag.
Paraskivi 15310, Athens, Greece.

ABSTRACT

As part of our project to develop small size, neutral, mixed ligand oxotechnetium and
oxorhenium complexes of the general formula MOL\textsubscript{1}L\textsubscript{2}, we have synthesized and characterized
four novel complexes of general formula MO[EtN(CH\textsubscript{2}CH\textsubscript{2}SH)]\textsubscript{2}[p-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{4}S] and MO
[(Et\textsubscript{2}NCH\textsubscript{2}CH\textsubscript{2}NCH\textsubscript{2}CH\textsubscript{2}SH)(p-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{4}S)] where M=Re (complex 1 and complex 2) or M=Tc
(complex 3 and complex 4) as a new approach for hypoxia or ischemic tissue organ imaging.
Complex 1 and 2 have been synthesized by exchange reaction in equimolar quantities of the
tridentate and the monodentate ligand on ReOCl\textsubscript{(PPh\textsubscript{3})}. Only the syn isomer have been isolated
and characterized by elemental analysis, IR, UV-vis, and \textsuperscript{1}\textsuperscript{H} NMR. Crystal datas reveal a trigonal
bipyramidal geometry around the metal for complex 1 and square pyramidal geometry around the
metal for complex 2. Complex 3 is prepared by exchange reaction using Tc-99m-glucoheptonate
as precursor and equimolar quantities of two ligands; EtN(CH\textsubscript{2}CH\textsubscript{2}SH)\textsubscript{2} and p-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{4}SH while
complex 4 is prepared by simultaneously reacting the Et\textsubscript{2}NCH\textsubscript{2}CH\textsubscript{2}NHCH\textsubscript{2}CH\textsubscript{2}SH and p-O\textsubscript{2}N-
C\textsubscript{6}H\textsubscript{4}SH ligands with the \textsuperscript{99m}Tc gluconate precursor in equimolar amount in MeOH.

It may be concluded that the result of SNS/S and SNN/S mixed ligand of oxotechnetium
is confirmed by comparative HPLC studies with complex 1 and complex 2, since rhenium is a
surrogate of technetium.
INTRODUCTION

Nitroimidazole derivatives labeled with a number of radionuclides, such as $^{123}$I, $^{11}$C and $^{18}$F, have been evaluated over the past few years as potential agents for the non-invasive imaging of hypoxia tissues. As far as $^{99m}$Tc is concerned, $^{99m}$Tc complexes based on the nitroimidazole-BATO or the (2-nitroimidazole)-1-PnAO system have demonstrated promising results in terms of selective localization in cerebral or myocardial ischemic tissue in animal models [1,2].

As part of our recent work on the development and evaluation of rhenium (V) and technetium (V) mixed ligand complexes with potential medical application, we report herein the synthesis and characterization of four novel complexes general formula MO[EtN(CH$_2$CH$_2$)$_2$S]$_2$[p-O$_2$N-C$_6$H$_4$S] and MO[(Et$_2$NCH$_2$CH$_2$NCH$_2$CH$_2$S)(p-O$_2$N-C$_6$H$_4$S)] where M=Re (complex 1 and complex 2) or M=Tc (complex 3 and complex 4). In both metal chelates a nitro group is introduced on the aromatic monothiolate ligand, expected to direct the radioactivity on the ischemic tissue in question acting as the radiosensitizer [3].

METHODS

- **Preparation of the Re complex, 1 and 2**: The complexes are produced by simultaneous action of EtN(CH$_2$CH$_2$SH)$_2$ or Et$_2$NCH$_2$CH$_2$NHCH$_2$CH$_2$SH and p-O$_2$N-C$_6$H$_4$SH ligands on the ReOCl$_3$(PPh$_3$)$_2$ in equimolar quantities in a refluxing AcONa methanolic solution. Dark-green and Red-brown crystals separate by slow evaporation from a CH$_2$Cl$_2$/MeOH mixture and are then characterized by elemental analysis, IR, UV, $^1$HNMR, HPLC and X-ray crystallography.

- **Preparation of $^{99m}$Tc complex 3**: Complex 3 is prepared by exchange reaction using EtN(CH$_2$CH$_2$SH)$_2$ and Tc-$^{99m}$-glucoheptonate as precursor and equimolar quantities of the two ligands. Only one complex, the syn isomer, is formed. Its identity is confirmed by comparative HPLC studies with complex 1, since rhenium is a surrogate of technetium.

- **Preparation of the $^{99}$Tc complex 4**: The analogous $^{99}$Tc complex 4 is prepared by simultaneously reacting Et$_2$NCH$_2$CH$_2$NHCH$_2$CH$_2$SH and p-O$_2$N-C$_6$H$_4$SH ligands with the $^{99}$Tc-gluconate precursor in equimolar amounts in MeOH. The crystalline product
precipitates by slow evaporation from \( \text{CH}_2\text{Cl}_2/\text{MeOH} \) mixture and are characterized by elemental analysis, IR, UV-Vis, \(^1\)H NMR and HPLC analysis.

- **HPLC comparision of complex 2 and 4**: Both Re and \(^{99}\)Tc complexes are injected on a RP C18 column, which is eluted with 85% MeOH and the complexes are monitored both by photometric and radiometric detection.

**RESULTS AND DISCUSSION**

Simultaneous action of equimolar amounts of \( \text{EtN(CH}_2\text{CH}_2\text{SH)}_2 \) or \( \text{Et}_2\text{NCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{SH} \) and \( p\text{-O}_2\text{N-C}_6\text{H}_4\text{SH} \) ligands on a suitable Re\(^{\text{V}}\) and \(^{99}\)Tc\(^{\text{V}}\) precursor leads to the formation of the isostructural complex 1, 2 and 4, according to equation [1] and [2].

\[
\text{M}^{\text{V}} \text{O} + \text{EtN(CH}_2\text{CH}_2\text{SH)}_2 + p\text{-O}_2\text{N-C}_6\text{H}_4\text{SH} \rightarrow 1 \quad \text{eq [1]}
\]

\[
\text{M}^{\text{V}} = \text{Re}
\]

\[
+ \text{Et}_2\text{NCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{SH} + p\text{-O}_2\text{N-C}_6\text{H}_4\text{SH} \rightarrow 2, 4 \quad \text{eq [2]}
\]

\[
\text{M}^{\text{V}} = \text{Re or } {^{99}\text{Tc}}^{\text{V}}
\]

Structure and purity of complex 1, 2, 4 are established by comparision of analytical (UV-Vis, IR, \(^1\)H NMR) data with that reported for other SNS/S and SNN/S complexes of established structure [4] and by X-ray structure analysis of complex 1 and complex 2.

Crystal data of complex 1 shows a trigonal bipyramidal geometry around the metal. An ORTEP diagram is given in Fig 1. The basal plane is defined by the sulfur atoms of the tridentate ligand and oxygen, while the two apical positions are occupied by the nitrogen of the tridentate ligand and the sulfur atom of the monodentate thiol.
Crystal structure analysis of complex 2 reveals that the compound adopts a distorted square pyramidal geometry around the metal. As shown in the ORTEP diagram of Fig 2, the SNN atoms of the aminothiolate tridentate ligand occupy the basal plane of the pyramid. The coordination sphere is completed by the sulfur atom of the monodentate thiol in the basal plane and the oxo group of the Re=O core positioned on the apex of the distorted square pyramid.
CONCLUSION

The chemistry of rhenium complexes was studied by spectroscopic method which has the identical property with technetium complexes. Thus Rhenium is a surrogate of technetium for chemical study while $^{99m}$Tc is used for biodistribution study. Further studies of $^{99m}$Tc complexes are made in progress in order to evaluate the behavior of the complex in experimental animals.

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