1 Introduction

The coordination chemistry of rhenium and technetium has constantly been attended due to the radionuclide-based application in radiopharmaceuticals. $^{99m}$Tc is the most common radionuclide used in diagnostic imaging because of its almost perfect physical properties ($E_\gamma = 140$ keV, $t_{1/2} = 6.02$ h) [1]. Moreover, its availability from commercial $^{99}$Mo/$^{99m}$Tc generator systems [2] makes technetium compounds very practical and convenient for routine use in the clinic. Recently, two isotopes of rhenium, $^{186}$Re ($E_{\text{max}} = 1.1$ MeV, $t_{1/2} = 90.64$ h) and $^{188}$Re ($E_{\text{max}} = 2.1$ MeV, $t_{1/2} = 17$ h) were introduced in nuclear medical research as suitable $\beta^-$ emitting radionuclides for the therapy of malignant and degenerative diseases [3,4]. In particular, the availability of a $^{188}$W/$^{188}$Re generator [5] makes $^{188}$Re one of the most promising candidate for the development of radiopharmaceuticals for use in radiotherapy. The challenge is the elucidation of the molecular structures of $^{99m}$Tc- and $^{186/188}$Re-based agents which are produced in very low concentrations at nanomolar scale. This may be achieved by the comparison of their chemical and physical properties with those of the corresponding compounds prepared at macroscopic scale with the long-lived isotope $^{99}$Tc and with natural rhenium. In addition, rhenium and technetium belong to the same group of the periodic table and, therefore, they show similar chemical properties and rhenium is often used as a non-radioactive alternative to technetium in chemical experiments.

Scheme 1 $^{99m}$Tc radiopharmaceuticals: $^{99m}$Tc-(HMPAO) (left) and $^{99m}$Tc(MIBI) (right).

Classical metal-containing radiopharmaceuticals mostly require thermodynamically stable or kinetically inert complexes. This can be achieved either with strong chelating or tightly bonded monodentate ligands [6,7]. More important is, especially for radiotherapy, that the complexes have sufficiently selective biodistribution, which limits the number of metal complexes which are useful as radiopharmaceuticals [6,7]. Two examples of $^{99m}$Tc complexes, which are currently used in clinic for myocardial or cerebral imaging, are $^{99m}$Tc-(HMPAO) (HMPAO = hexamethyl propyleneamine oxime) [8], and $^{99m}$Tc(MIBI) (MIBI = 2-methoxy-2-methylpropyl-isonitrile) [9] (Scheme 1). A modern trend in rhenium and
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Technetium radiopharmaceutical chemistry is the labelling of biomolecules, which uses stable complexes of the radioactive metals with bifunctional chelators. They can covalently be bonded to a targeting molecules, such as a monoclonal antibody, a peptide, or other biologically active molecules. Such radiopharmaceuticals are able to target specific receptor sites in the body [10].

In this context, there is a continuous need for efficient ligand systems. Ligands, which are suitable for the stabilization of the \( \{M^\text{V}=\text{O}\}^{3+} \) or \( M^{3+} \) cores (\( M = \text{Re, Tc} \)) are of particular interest, since reduction of \([\text{MO}_4^-]\) ions from the commercial generator systems with common reducing agents frequently form such species. Thioureas are known to possess an affinity to various rhenium and technetium cores with the metals in different oxidation states [11]. The complexes of thiourea derivatives such as aroylthioureas and benzamidines are more stable due to the chelate effect. While the coordination chemistry of bidentate benzamidines with rhenium and technetium is well explored, only two aroylthiourea rhenium complexes, \([\text{ReOCl} (\text{Et}_2\text{btu})_2] \) (Ic) and \([\text{Re(CO)}_3\text{Br(HEt}_2\text{btu})_2] \), where \( \text{HEt}_2\text{btu is } N'\text{-N'-diethyl-N-}

benzoylthiourea, are hitherto reported [12,13]. Furthermore, the benzamidine system has many opportunities to be extended to higher denticity such as to tri-, tetra- or pentadentate systems. However, this area is almost unexplored. Only one tetradenate thiocarbamoyl benzamidine derived from o-phenylenediamine and its copper and nickel complexes are previously published [14,15]. Nevertheless, the facile variation of substituents of the thiourea moiety in both aroylthioureas and benzamidines gives convenience in tuning their chemical and physical properties and also in the introduction of additional functional groups used for the coupling of biomolecules.

This thesis introduces stable complexes of rhenium and technetium with aroylthiourea and benzamidine ligand systems. In order to fulfil this aim, polydentate benzamidine systems with up to five donor atoms were synthesized. Both fundamental coordination chemistry and potential applications in chemotherapy and in radiopharmaceutical agents are studied.