Journal of Organometallic Chemistry 751 (2014) 83–89

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Review

Rhenium and technetium based radiopharmaceuticals: Development and recent advances

Sophie Jürgens, Wolfgang A. Herrmann*, Fritz E. Kühn*

Chair of Inorganic Chemistry/Molecular Catalysis, Catalysis Research Centre of the Technische Universität München, Ernst Otto Fischer-Str. 1, 85747 Garching bei München, Germany

ARTICLE INFO

Article history:
Received 31 May 2013
Received in revised form
12 July 2013
Accepted 15 July 2013

Keywords:
Rhenium
Technetium
Radiopharmaceuticals
Molecular imaging
Targeting
Review

ABSTRACT

The higher homologues of group 7 transition metals, namely technetium and rhenium, offer radioisotopes suitable for the application as radiopharmaceuticals. Three generations of radiopharmaceuticals have been applied so far, with two of them reaching clinical application. While the first generation does not display a target specific functionality to bind exclusively to one (or few) targets, the second generation allows target specific binding. The synthesis, however, is more sophisticated, but allows in principle a "Lego brick" build up of a radioactive moiety, a linker and a binding moiety. The third generation aims at an "all in one approach", an organometallic derivative of a "key", fitting to a specific receptor that also carries the "load" of the radioactive molecule. Although most elegant from design, such molecules are most difficult to develop. With the many available organometallic and inorganic rhenium derivatives, however, at least a much larger variety of specific "second generation" radiopharmaceuticals should be available.

Contents

1. Introduction

Recently group 7 transition metal complexes with *N*-heterocyclic carbenes ligands were reviewed [1]. Numerous reviews and book articles highlighting the synthesis and application of rhenium and technetium based radiopharmaceuticals have also been published, providing good overviews on the developments preceding their publication [2–8]. However, many organometallic chemists are still unaware of the possibilities their newly synthesized compounds might offer for medicinal applications. The intention of this review is to compile the latest advances concerning the targeted tumor therapy based on organometallic and inorganic building blocks, especially focusing on dextran derivatives utilizing a *fac*-$[M(CO)_3]^+$ core.

Effective therapy and molecular imaging of tumors continues to be one of the most important challenges of current clinical research. Radiopharmaceuticals present thereby a noninvasive alternative for rapid detection of tumor tissue. Therapy is carried out tumor specifically and therefore at significantly lower radioactive doses as for conventional chemotherapy. A broad variety of rhenium and technetium based radiopharmaceuticals has been

* Corresponding authors. Tel.: +49 (0)89 289 13096.
E-mail addresses: wolfgang.herrmann@ch.tum.de (W.A. Herrmann), fritz.kuehn@ch.tum.de (F.E. Kühn).

0022-328X/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jorganchem.2013.07.042

reported since the first experimental application of $^{99m}TcO_4^-$ for imaging of the thyroid in 1961 [9,10]. This mirrors the fact that rhenium and technetium as group 7 elements can exist in oxidation states from (+VII) to (−I) and therefore display rich coordination chemistry.

Radiopharmaceuticals are applied *in vivo* for imaging of tumors and/or radionuclide therapy. The respective utilization of a radioisotope depends on its radioactive nature; whereas γ or β^+ emitters are used in diagnostic nuclear medicine, β^-, α- or Auger electron emitters are used for tumor-specific therapy [11]. The targeted radionuclide therapy (TRT) bases thereby on the localization of tumor tissue by the ionizing radiation emitting radionuclides [12]. In contrast to chemotherapy, this radiation is specifically cytotoxic to tumor tissue cells and does not attack surrounding healthy cells. However, neither the amounts of adsorbed radiation doses needed for successful TRT, nor the tolerance doses for healthy tissues cells are exactly defined. A main point of overcoming this problem would be a full understanding of the pharmacokinetics of the therapeutical radionuclide agent [13–15].

Imaging of tumor tissue is mainly performed by single photon emission computed tomography (SPECT) and positron emission tomography (PET). These gamma imaging techniques enable a very accurate examination of the interaction between the applied radiopharmaceutical and the targeted tumor tissue. Furthermore, they offer a quantitative approach on monitoring the doses of radionuclides taken into tumor tissue [16–18]. The application of either of these high-resolution molecular imaging techniques depends on the respective isotope. While PET uses light isotopes, e.g. ^{18}F or ^{15}O, SPECT demands heavy isotopes such as ^{131}I and ^{67}Ga. For PET most isotopes are generated via a cyclotron and subsequently incorporated into biologically active molecules. Most widely applied is fluorodeoxyglucose (^{18}F-FDG), making up for the majority (approximately 90%) of all PET applications [19]. Moreover, PET offers a significant higher imaging sensitivity of up to three orders of magnitude than SPECT due to its higher photon detection efficiency [20]. However, with SPECT longer imaging intervals can be performed, as single photon emitters have a longer half-life time. This enables the observation of *in vivo* processes for several hours or even days. Plus the longer lifetime of the isotope makes SPECT a less expensive imaging technique than PET. SPECT mainly applies ^{99m}Tc for various application fields such as neurochemical or myocardial imaging [21]. In recent years the use of a hybrid technique with computed tomography (CT) has aroused interest as the imaging accuracy of SPECT and PET could be enhanced. More potent SPECT/CT and PET/CT systems have been introduced, which incorporate multi-slice CT (up to 16 slices), allowing diagnostic CT images [22]. This stresses the fact that not only isotope tracers, but also the development of the imaging modalities are of crucial importance for the future development of radiopharmaceutical chemistry.

^{99m}Tc is considered as the "workhorse" for radiopharmaceutical imaging. Its long-lived isotope ^{99}Tc (half-life time 2.12×10^5 years) is a β^- emitter and is formed as a fission product in nuclear reactors. The use of ^{99m}Tc displays three major advantages: (i) a γ-energy of 140 keV which penetrates tumor tissue while simultaneously presenting a relatively low radiation dose, (ii) a half-life time of 6 h, ensuring reasonable medical imaging intervals and (iii) readily availability at low costs from $^{99}Mo/^{99m}Tc$ generators [23].

First introduced in 1965 for clinical application, the $^{99}Mo/^{99m}Tc$ isotope generator is the main source for ^{99m}Tc (see Fig. 1) [24].

The parent isotope ^{99}Mo, processed as molybdate $[^{99}MoO_4]^{2-}$, is loaded onto an alumina chromatography column and ^{99m}Tc is isolated in great quantity as pertechnetate $[^{99m}TcO_4]^-$ by elution with a 0.15 M saline solution.

The β^- emitting radionuclides ^{188}Re ($t_{1/2} = 16.9$ h, $E_{max} = 2.1$ MeV) and ^{186}Re ($t_{1/2} = 89.2$ h, $E_{max} = 1.1$ MeV) can be isolated in an analogous fashion from a ^{188}W generator system [25]. Both rhenium radionuclides allow an effective energy transfer to cancer tissue; however ^{188}Re is mostly favored due to its more convenient half-life time. The isotope generators enable a preparation of the respective radiopharmaceuticals directly in hospitals, ensuring a constant availability. Those preparations are therefore carried out in saline, with the permetallate as starting material.

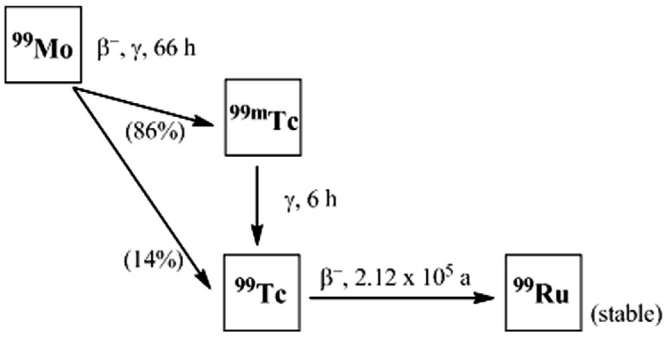

Fig. 1. Decay of ^{99}Mo in the $^{99}Mo/^{99m}Tc$ generator.

Rhenium and technetium pharmaceuticals are organ specific; thus the demands on chemical structure and *in vivo* behavior can vary strongly. Through choice of ligands, the specific biological moieties and physiochemical properties of the respective radiopharmaceutical can be fine-tuned.

2. Overview of rhenium and technetium radiopharmaceuticals

The rhenium and technetium based radiopharmaceuticals can be divided up into three generations, relating to their biological distribution pattern or respective synthetic approach.

2.1. First generation radiopharmaceuticals

The majority of all commercially established, technetium based imaging agents belongs to the first generation of radiopharmaceuticals. These complexes are perfusion agents and do not display targeting functions. The ligand system is biologically inactive without the metal center, therefore first generation radiopharmaceuticals are also referred to as "technetium/rhenium essentials" or *de novo* compounds [26].

Preparation of first generation radiopharmaceuticals is carried out via so-called "instant kits", with the permetallate added directly before *in vivo* injection. These kits contain the ligand system, a reducing agent (typically a Sn(II) salt), buffer to adjust the pH to labeling conditions, stabilizers and catalysts [27,28]. The ligand system stabilizes thereby the lower oxidation state of the Lewis acidic metal center and determines its biological distribution.

The field of application for first generation pharmaceuticals is mainly determined by their physiochemical properties such as hydrophilicity, charge and size of the complex. These properties are believed to determine the biological distribution of the radiopharmaceutical between tissues [29]. A full explanation for the biological distribution and pharmacokinetic path of first generation radiopharmaceuticals has yet to be found.

One of the first technetium-based radiopharmaceuticals were ^{99m}Tc-gluconates and ^{99m}Tc-glucoheptonates [30]. They were introduced for renal clearing studies, as they display the high hydrophilicity, which is mandatory for renal imaging in order scans the delivery of fluid into the kidneys via the bloodstream concentration [6]. Yet the excretion through the kidneys is too slow do to