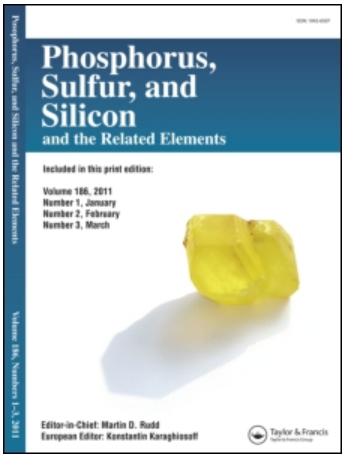

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Bifunctional Chelation Systems Based on Hydroxymethyl Phosphine-Based Donor Groups

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Chelating frameworks based on hydroxymethylene phosphine (HMP) functionalities provides a novel approach to produce chelate-conjugates compatible with development of new Tc-99m and Re-186/188 radiopharmaceuticals. Studies with a bombesin conjugate demonstrates the potential of using HMP-based chelating frameworks to develop radiolabeled receptor-avid agents for targeting cancers.

Keywords: hydroxymethylenephosphine; bioconjugates; radiopharmaceuticals; cancer; Technetium-99m

INTRODUCTION

Opportunities are steadily increasing for designing site-directed bioconjugates that will provide for future advances in diagnosis and treatment of human cancers. Many biomolecular vectors and their cognate molecular targets, which are uniquely or over-expressed on cancer cells, are being identified and characterized. Formulation of radiolabeled vectors via conjugation of a well defined radiometal chelate can provide for effective cancer targeting radiopharmaceuticals. In most cases, the physico-chemical properties of the metal chelate system plays an essential role in determining the *in vivo* localization properties of these radiolabeled agents. Technetium-99m (^{99m}Tc) is the most widely used radionuclide for diagnostic Nuclear Medicine studies while its chemical congener, rhenium-186/188 ($^{186/188}$Re), holds potential for therapeutic applications. For this reason, it is essential that chelating frameworks capable of forming well defined and stable ^{99m}Tc (and Re) chelates be developed that can be used to formulate more effective cancer specific ^{99m}Tc/$^{186/188}$Re radiopharmaceuticals.

Phosphine ligands have been successfully used to produce ^{99m}Tc-labeled chelates for applications in Nuclear Medicine for two decades[1]. However, their utility in

formulating phosphine groups containing bioconjugates has been limited, primarily due to the oxidative instability of alkyl phosphine or the bulky size of arylphosphine groups. Since hydroxymethylene phosphine (HMP) groups exhibit good stability toward air oxidation in aqueous solutions and coordinate strongly with both Tc and Re, they are attractive for use in formulating new ^{99m}Tc- and $^{186/188}$Re-bioconjugates.

Results and Discussion

Only very few chelating frameworks (incl., N_3S, N_2S_2, and HYNIC systems) have been developed that are useful in synthesizing a limited spectrum of site-specific ^{99m}Tc/Re-bioconjugates[2] making it essential to identify others. Over the past few years, the potential of using HMP-based ligand structures in conjunction with ^{99m}Tc and $^{186/188}$Re has been explored[3,4]. Novel approaches have been developed to synthesize new multidentate HMP containing ligands. As a result of this work, the first HMP based bifunctional chelating agent (BFCA) was synthesized[5]. This BFCA is diphosphine-dithia (P_2S_2) ligand system to which a side chain containing a -COOH group is appended (See Figure 1).

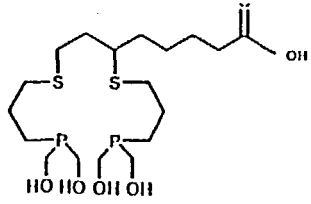

Figure 1. P_2S_2-BFCA

Studies with this BFCA showed that the P_2S_2 moiety complexes with the Re(V) *trans* dioxo core, leaving the -COOH group available for use in linking amine groups on various biomolecules (incl., proteins and peptides). Parallel studies with ^{99m}Tc showed that the corresponding [^{99m}Tc]Tc(V)O_2^+-P_2S_2-BFCA chelate is formed in high radiochemical purity and exhibits high *in vitro* and *in vivo* stability in the acidic and

neutral pH ranges[6]. It is also important to note that ^{99m}Tc-P_2S_2 complexes can be produced in high yields using only 10^{-5}M P_2S_2-BFCA concentrations enabling formation of high specific activity ^{99m}Tc-products. Activation of the -COOH group on the "preformed" ^{99m}Tc/Re-P_2S_2-BFCA with pentafluorophenol (PFP), or other similar activating reagents, produces a robust intermediate that can be used to form an amide linkage with amine groups on biomolecules[7]. Recent studies with a bombesin (BBN) analogue, a receptor-avid peptide, demonstrate that the PFP activated ^{99m}Tc/Re-P_2S_2-BFCA can be efficiently conjugated to the N-terminal amine group on BBN(7-14)[8]. The structure of the ^{99m}Tc- and corresponding Re-P_2S_2-BBN(7-14) conjugate formed in these studies is shown in Figure 2.

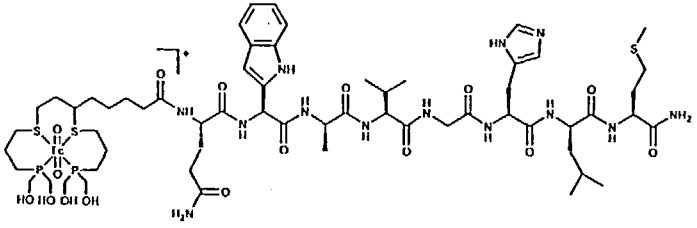

Figure 2. Structure of ^{99m}Tc-P_2S_2-BBN Conjugate

In vitro cell binding studies using Swiss 3T3 cells show that Re-P_2S_2-BBN(7-14) retains high specific binding affinity (i.e., IC_{50} = 0.77 ± 0.40 nmolar relative to ^{125}I-Tyr^4-BBN) for BBN receptors expressed on these cells. The corresponding ^{99m}Tc-P_2S_2-BBN(7-14) (Figure 2) also demonstrated high *in vitro* binding affinity to BBN receptors and specific *in vivo* targeting of BBN receptor expressing cells in a CF-1 mouse model. For example, at four hours post-injection, the deposition of ^{99m}Tc activity in the pancreas (pancreatic acini cells express BBN receptors) was high with pancreas to blood and pancreas to muscle ratios reaching 22.3 and 79.1[7]. Pharmacokinetic studies indicates high *in vivo* stability of the ^{99m}Tc-P_2S_2 conjugate and good clearance from non-target tissues and organs. The results of these studies in animals coupled with chemical

and *in vitro* systems demonstrate the feasibility of using HMP-based chelating systems to form ^{99m}Tc (and $^{186/188}$Re) bioconjugates that can be used to formulate site-specific targeting of human cancerous tumors. It is important to recognize that the P_2S_2-ligand framework used in these studies is the first example of a HMP-based ligand system for use in producing ^{99m}Tc/$^{186/188}$Re bioconjugates. Future HMP-based ligand systems (e.g., P_2N_2 frameworks) will provide increased flexibility for conjugate design and may offer avenues for improved performance.

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