**Title:** STABILIZATION OF RADIOPHARMACEUTICAL COMPOSITIONS USING HYDROPHILIC THIOETHERS AND HYDROPHILIC 6-HYDROXY CHROMANS

**Abstract:** Radiopharmaceutical compositions which are stabilized by addition of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative.
STABILIZATION OF RADIOPHARMACEUTICAL COMPOSITIONS
USING HYDROPHILIC THIOETHERS AND HYDROPHILIC 6-HYDROXY
CHROMANS

The present invention relates to novel stabilizers of radiopharmaceutical compositions used for diagnosis and therapy. In particular, the invention relates to use of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, or a combination of a hydrophilic thioether with a hydrophilic 6-hydroxy-chroman derivative, to increase the shelf-life of diagnostic and therapeutic radiopharmaceuticals.

A number of radionuclides are routinely employed in nuclear medicine, both as diagnostic agents and as therapeutics. For example, $^{99m}$Tc, $^{111}$In, $^{18}$F, and $^{201}$TI are employed as diagnostic imaging agents, and $^{131}$I, $^{32}$P, $^{89}$Sr, and $^{153}$Sm are in therapeutic use. In addition, nuclides such as $^{186}$Re, $^{188}$Re, $^{212}$Bi, $^{213}$Bi, $^{90}$Y, $^{67}$Cu, $^{192}$Ir, $^{165}$Dy, and $^{117m}$Sn have been proposed as potential therapeutic agents. Such radionuclides are administered in the form of radiopharmaceutical compositions, which generally include a chelator for the nuclide. Radiopharmaceuticals may additionally include a targeting molecule such as a monoclonal antibody, an antibody fragment, or a receptor ligand. The availability of radiopharmaceuticals has significantly advanced diagnosis and treatment of a variety of diseases.

Chemical decomposition may limit a radiopharmaceutical’s shelf life by decreasing the radiochemical purity of the agent over time. For example, a radiopharmaceutical containing $^{99m}$Tc, $^{186}$Re, or $^{188}$Re may be susceptible to oxidation of the nuclide itself. In addition, the radiation emitted from a radionuclide can break chemical bonds of other components of the composition, thus causing autoradiolysis. Autoradiolysis is a particular problem when the radiopharmaceutical contains higher energy nuclides, such as $\beta$-emitters (e.g., $^{186}$Re, $^{188}$Re, $^{90}$Y, $^{121}$I) and $\alpha$-emitters (e.g., $^{213}$Bi, $^{212}$Bi, $^{211}$At, $^{225}$Ac, $^{223}$Ra).

Thus many radiopharmaceuticals require stabilizers to maximize shelf life. Such stabilizers must be non-toxic and must be able to maintain the product’s radiochemical purity for an acceptable shelf-life as well as during use. In addition, an acceptable
radiopharmaceutical stabilizer must not interfere with delivery of the radionuclide to the target site.

Methods for stabilizing radiopharmaceuticals by adding gentisates are disclosed, for example, in U.S.Pat.Nos. 4,232,000; 4,233,284; 4,497,744; 5,384,113. Stabilization of radiopharmaceuticals using ascorbic acid is disclosed in U.S.Pat.Nos. 5,393,512 and 5,011,676, in WO 97/28181 and in WO 98/33531. Hydroquinone stabilizers of radiopharmaceuticals is disclosed in U.S.Pat.No. 4,229,427. Other compounds such as reductic acid, erythorbic acid, p-aminobenzoic acid, 4-hydroxybenzoic acid, nicotinic acid, nicotinamide, 2,5-dihydroxy-1,4-benzenedisulfonic acid, tartaric acid, inositol, and the like, have also been used to stabilize radiopharmaceutical compositions.

U.S.Pat.No. 5,384,113 discloses a method of preventing autoradiolysis of peptides radiolabeled with $^{111}$In using gentisic acid or gentisyl alcohol. In addition to preventing autoradiolysis of peptides by $^{111}$In, the method of U.S.Pat.No. 5,384,113 is proposed to prevent autoradiolysis of peptides by $^{67}$Ga, $^{185}$Yb, $^{123}$I, $^{123}$I, and $^{203}$Tl. Two radiolabelled peptides, $^{111}$In-DTPA-octreotide and $^{123}$T-LHRH, were tested for autoradiolysis prevention. A monoclonal antibody, NR-Lu-10, labeled with $^{186}$Re was also specifically exemplified.

As indicated in Example 1, infra, the present inventors have found that that when added as a component in radiopharmaceutical kit formulations, gentisic acid decreases the radiochemical purity of some $^{99m}$Tc-labelled peptides, and thus is not useful as a stabilizer of some radiolabeled peptides. A need exists, therefore, for additional stabilizers of radiopharmaceuticals. A particular need exists for stabilizers of radiopharmaceuticals containing less than 70 amino acids linked by peptide bonds.

Methionine residues in proteins and polypeptides are known to oxidize to methionine sulfoxide. U.S.Pat.No. 5,272,135 discloses a method of inhibiting oxidation of a liquid or semi-liquid composition of a polypeptide containing at least one methionine residue by adding between 0.01% w/v to 0.3% w/v methionine to the composition. U.S.Pat.No. 5,272,135 teaches that the method disclosed therein is effective with a variety of polypeptides, including epidermal growth factor, insulin-like growth factor I, nerve growth factor, transforming growth factor alpha precursor, transforming growth factor beta precursor, transforming growth factor beta, fibroblast growth factor, vaccinia growth
factor, platelet derived growth factor, or methionine containing biologically active fragments or precursors of such growth factors. However, the data presented in U.S.Pat.No. 5,272,135 are limited to addition of methionine to inhibit oxidation of methionine residues present in epidermal growth factor. Lam, et al. (1997) J. Pharm. Sci. 86, 1250-1255 disclose the use of methionine to stabilize the recombinant humanized monoclonal antibody rhuMAb HER2 in liquid formulations to prevent oxidation of methionine residues.

U.S.Pat.No. 5,358,708 discloses a method for increasing the storage stability of an aqueous formulation of granulocyte-macrophage colony stimulating factor or an interleukin by addition of a stabilizing amount of methionine, histidine, or mixtures thereof. U.S.Pat.No. 5,358,708 also discloses that chemical differences among proteins cause different proteins to become inactivated during storage at different rates and under different conditions. U.S.Pat.No. 5,358,708 further discloses that the storage-prolonging effects of methionine and histidine are not equivalent with different proteins, and that mixtures of amino acids exhibit different effects as the ratio varies, as the identity of the protein is changed, and/or as concentrations are altered.

WO 97/14430 discloses use of hydrophilic thioethers as antioxidants to prolong storage stability of aqueous formulations of proteins and peptides. The only data presented in WO 97/14430 relate to insulin-like growth factor I, a 70-amino acid peptide containing three disulfide bonds. WO 97/14430 further discloses that common antioxidants such as ascorbic acid, sodium thiosulfate, glutathione, or sodium bisulfite increased oxidation of IGF-1 or even precipitated the protein.

U.S.Pat.Nos. 3,947,473; 4,003,919; 4,018,799; and 4,026,907 disclose a variety of antioxidant hydrophilic 6-hydroxy-chroman compounds as intermediates in preparation of optically active α-tocopherol. U.S.Pat.No. 4,511,685 discloses hydrophilic 6-hydroxy-chroman derivatives and use of such derivatives to stabilize polypropylene compositions. U.S.Pat.Nos. 4,847,267 and 4,970,216 disclose use of one such hydrophilic 6-hydroxy-chroman, hydrophilic 6-hydroxy-2,5,7,8-tetramethyl-2-carboxylic acid alone or in combination with sulfur compounds, including glutathione or cysteine, as a skin treatment composition to inhibit generation of free radicals in the skin.
It has now been surprisingly found that the radiolabelling efficiency and shelf-life of peptide and non-peptide radiopharmaceutical compositions may be significantly increased by addition of a stabilizing amount of a hydrophilic thioether, a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative, or a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman.

In the first aspect of this invention, the radiolabelling efficiency and shelf life of the radiopharmaceutical compositions are increased by the addition of a hydrophilic thioether.

In one embodiment of this first aspect, the invention provides a composition comprising a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic thioether.

In another embodiment of this first aspect, the invention provides a method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic thioether in a container; and

b) adding a radionuclide to the container.

In another embodiment of this first aspect, the invention provides a kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic thioether.

In a second aspect of this invention, the radiolabelling efficiency and shelf life of the radiopharmaceutical compositions are increased by the addition of a hydrophilic 6-hydroxy-chroman derivative.

In one embodiment of this second aspect, the invention provides a composition comprising a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative.

In another embodiment of this second aspect, the invention provides a method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative in a container; and

b) adding a radionuclide to the container.
In another embodiment of this second aspect, the invention provides a kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative.

In the third aspect of this invention, the radionabelling efficiency and shelf life of the radiopharmaceutical compositions are increased by the addition of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative.

In one embodiment of this third aspect, the invention provides a composition comprising a radiopharmaceutical precursor, a hydrophilic thioether, and a hydrophilic 6-hydroxy-chroman.

In another embodiment of this third aspect, the invention provides a method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman in a container; and

b) adding a radionuclide to the container.

In another embodiment of this third aspect, the invention provides a kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman.

As defined herein, a “radiopharmaceutical” or “radiopharmaceutical composition” comprises a radionuclide, a chelator, and optionally a targeting moiety or domain.

In accordance with the invention, a “precursor” of a radiopharmaceutical is defined as comprising an unlabelled, that is, non-radioactive, reagent which may be a chelator or a chelator covalently linked to a targeting moiety or domain.

A “targeting moiety or domain” as defined herein as a moiety or domain capable of binding specifically to a site within a mammalian body such as a receptor on a cell surface. Targeting moieties or domains within the scope of the present invention include but are not limited to antibodies, antibody fragments such as Fab or F(ab)₂ fragments, epitope binding complementarity determining regions derived from antibodies, peptides, growth factors or receptor binding fragments thereof, hormones, steroids, receptor binding nucleic acids, receptor binding carbohydrates including monosaccharides,
disaccharides, and oligosaccharides, receptor-binding lipids, benzodiazepines, receptor binding antibiotics, and the like.

A “stabilizing amount” is defined herein as that amount of hydrophilic thioether, hydrophilic 6-hydroxy-chroman or hydrophilic thioether/hydrophilic 6-hydroxy-chroman mixture sufficient to maintain the radiochemical purity, as measured by known methods such as those disclosed in the examples below, of a radiopharmaceutical composition relative to that of the radiopharmaceutical composition without the additive for at least 3 hours. Preferably, a clinically acceptable radiochemical purity for a radiopharmaceutical is at least 80% of the labelled undegraded radiopharmaceutical. More preferably, a clinically acceptable radiochemical purity for a radiopharmaceutical is at least 85% of the labelled undegraded radiopharmaceutical. Most preferably, a clinically acceptable radiochemical purity for a radiopharmaceutical is at least 90% of the labelled undegraded radiopharmaceutical.

Preferably, a stabilizing amount of hydrophilic thioether is in the range of about 0.1% (w/v) to about 1.5% (w/v). More preferably, a stabilizing amount of hydrophilic thioether is in the range of about 0.4% (w/v) to about 1.0% (w/v). More preferably, a stabilizing amount of hydrophilic thioether is in the range of about 0.5% (w/v) to about 1.0% (w/v).

A “hydrophilic thioether” is defined in accordance with the present invention as a compound having the general structure:

\[ R - S - CH_2C(R^1R^2R^3) \]

wherein:

R is C_1 to C_4 alkyl or a C_1 to C_4 alkyl containing at least one hydrophilic group selected from –COOH, –NH_2, –NHR^4, –NR^4_2, –OH, –SO_2R^4, –SOR^4, –SO_3H, –CONH_2, –CONHR^4, –CONR^4_2, –COOR^4, –OR^4, –SR^4, –NO_2, –SO_2NH_2, –SO_2NHR^4, and –SO_2NR^4_2, with the proviso that, when R is methyl, the hydrophilic group is not NH_2, NHR^4, NR^4_2 or OH;

R^1, R^2, and R^3 are each independently selected from the group consisting of H, –COOH, –NH_2, –NHR^4, –NR^4_2, –OH, –SO_2R^4, –SOR^4, –SO_3H, –CONH_2, –CONHR^4, \ldots

C_1 to C_4 alkyl, and a C_1 to C_3 alkyl containing at least one hydrophilic group selected from \ldots
-COOH, -NH₂, -NHR
, -NR₂, -OH, -SO₂, -SO₃R
, -SO₃H, -CONH₂, -CONHR
, -CONR₂, -COOR
, -OR
, -SR
, -NO₂, -SO₂NH₂, -SO₂NHR
, and -SO₂NR₂, with the proviso that only one of R₁, R₂, and R₃ is -NH₂, NHR
, NR₂ or OH; and
R
 is selected from the group consisting of C₁ to C₃ alkyl;

and with the further proviso that the hydrophilic thioether comprise at least one of said hydrophilic groups. Specific hydrophilic thioethers of the present invention include D-methionine, L-methionine, D-ethylthione, L-ethylthione, 3-methylthio-1,2-propanediol, methyl-3-(methylthio)propionate, 2-(ethylthio)ethylamine•HCl, 2-(methylthio)-ethanol, buthionine, S-methyl-L-cysteine, S-methyl-D-cysteine, D-methioninol, L-methioninol, and the like. Preferably, the hydrophilic thioether used in the compositions of the invention is methioninol, 2-(ethylthio)-ethylamine•HCl, 3-methylthio-1,2-propanediol, or methionine.

More preferably, the hydrophilic thioether used in the compositions of the invention is 2-(ethylthio)-ethylamine•HCl or methionine. Most preferably, the hydrophilic thioether used in the compositions of the invention is L-methionine.

A “hydrophilic 6-hydroxy-chroman derivative” is defined in accordance with the present invention as having a formula:

Wherein one of Y and Z is selected from the group consisting of O, S, C=O, and (CHR
)_₃, where n is an integer from 0-3, and the other of Y and Z is selected from the group consisting of C=O and (CHR
)_₃, where n is an integer from 0 to 3;

each R
 group is independently selected from the group consisting of H, alkyl, halogen, -OR
, -SO₂H, -SO₃R
, -S(O)nR
, -COOR
, -NO₂,

-CONH_m(R
)_2-m, -NH_m(R
)_2-m, -COR
, -CH₂OR
, -COR
, -SO₂NH_m(R
)_2-m, -R
, and -CH₂R
, where m is an integer from 0 to 2;
R\(^4\) is H or C\(_1\) to C\(_3\) alkyl; and
R\(^3\) is selected from the group consisting of a monosaccharide, a disaccharide, and a hydrophilic peptide
sequence of up to 5 amino acids comprising at least one
hydrophilic amino acid residue.

Preferably, Y is (CH\(_2\)) and Z is (CH\(_2\)). Exemplary hydrophilic 6-hydroxy-chroman
derivatives of the present invention include 6-hydroxy-2,5,7,8-tetramethylchroman-2-
carboxylic acid (Trolox\(^\circledR\), available from Aldrich Chemical Co., (Milwaukee, Wisconsin,
USA); 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid-4-sulfonic acid; 6-
hydroxy-2,5,7,8-tetramethylchroman-3-hydroxy-2-carboxylic acid; 6-hydroxy-2,5,7,8-
tetramethylchroman-2-glucosamine, having a structure:

![Chemical structure 1]

and 6-hydroxy-2,5,7,8-tetramethylchroman-2-(carboxy-seryl-seryl-serylamide), having
the structure:

![Chemical structure 2]

Preferably, the hydrophilic 6-hydroxy-chroman derivative of the present invention is a
water soluble vitamin E derivative. More preferably, the hydrophilic 6-hydroxy-chroman
derivative of the invention is a 6-hydroxy-2,5,7,8-tetramethyl-2-carboxylic acid
derivative having –CH\(_2\) at the 3- and 4- positions and a hydrophilic substituent at the 2-
position. Most preferably, the hydrophilic 6-hydroxy-chroman derivative of the invention is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

Any radiopharmaceutical may be stabilized by addition of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman as taught herein. Ligand-type radiopharmaceuticals which do not comprise a targeting moiety or domain, such as Tc 99m MAG3 (TechnoScan®, Mallinkrodt Medical, Inc., St. Louis, Missouri, USA), may be stabilized in accordance with the present invention. In addition, radiopharmaceuticals comprising any kind of targeting moiety or domain may be stabilized in accordance with the present invention.

Recently a new class of radiopharmaceuticals has been developed which target a radiolabel to a particular tissue, disease site, or organ through a small receptor-specific molecule, which may be a peptide, a β-glucan, a benzodiazepine, or other small molecule. Such radiopharmaceuticals are disclosed and claimed, for example, in commonly assigned U.S. Pat. Nos. 5,508,020; 5,225,180; 5,405,597; 5,443,815; 5,552,525; 5,561,220; 5,620,675; 5,645,815; 5,654,272; 5,681,541; 5,711,931; 5,714,579; 5,716,596; 5,736,122; 5,770,179; 5,783,170; 5,788,960; 5,807,537; 5,807,538; 5,811,394; 5,814,297; 5,814,298; 5,814,299; 5,820,845; 5,820,846; 5,830,856; 5,833,942; 5,843,401; 5,843,403; 5,849,260; 5,849,261; 5,851,509; 5,866,097; 5,871,711; 5,932,189; 5,951,964; 5,955,426; 5,976,496; 5,997,844; 6,007,792; 6,017,509; 6,017,512; 6,028,056; 6,051,206; 6,074,627; 6,086,850; 6,171,178 and; 6,241,960; and in commonly assigned copending U.S. patent application numbers 08/236,402; 08/253,973; 08/721,443; and 09/553,494. These new agents comprise a chelator covalently linked to the receptor-specific targeting moiety or domain, and a radiolabel complexed with the chelator. A kit for making one such agent, ACUTECT®, has received approval in the U.S. for scintigraphic imaging of acute deep vein thrombosis. A second kit, NEOTECT®, has been approved in the U.S. for imaging malignant lung tumors. The stabilizers of the present invention are particularly suitable for use with radiopharmaceuticals which comprise chelators covalently linked to peptide, β-glucan, benzodiazepine, or other small targeting molecules as described in the commonly assigned patents and copending applications listed above.
In general, radiopharmaceuticals containing precursors in which a targeting moiety or domain is covalently linked to a monoamine, diamide, single thiol containing chelator such as those disclosed in commonly assigned copending U.S. patent application serial number 08/253,973 and in WO 95/33497 are stabilized using a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman in accordance with this invention. In addition, radiopharmaceuticals containing precursors in which a targeting moiety or domain is covalently linked to a bisamine bisthiol (BAT) chelator such as those disclosed in commonly assigned U.S.Pat.Nos. 5,780,007; 5,776,428; 5,720,934; 5,922,303; 5,965,107; 6,086,849; and 6,093,383 and in WO 93/21962 may be stabilized in accordance with the present invention.

The stabilizers of the present invention may also be used for radiopharmaceuticals comprising targeting molecules covalently linked to any chelator, such as the diamine monoamide thiol chelators and the triamine thiol chelators described in U.S.Pat.No. 5,688,485 and the triamine thiols disclosed in U.S.Pat.No. 5,091,514.

The stabilizers of the invention are preferably employed to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a peptide metal chelator having a formula

\[ C(pgp)^{\text{8}}-(aa)-C(pgp)^{\text{8}} \]

wherein \((pgp)^{\text{8}}\) is H or a thiol protecting group and \((aa)\) is an amino acid. Such chelators are disclosed and claimed in commonly assigned U.S.Pat.Nos. 5,654,272; 5,681,541; 5,788,960; and 5,811,394.

The stabilizers of the invention may also be employed to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a peptide metal chelator having a formula selected from the group consisting of:

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{CO--(amino acid)--cysteine--CO--} \\
\end{array}
\]

\[
\text{SX}
\]

wherein \(X\) is H or a protecting group;

(amino acid) is any amino acid;

and
wherein \( X \) is H or a protecting group;

wherein (amino acid) is any amino acid.

Such chelators are disclosed and claimed in commonly assigned U.S. Pat. Nos. 5,720,934; 5,776,428; 5,780,007; 6,086,849 and 6,093,383.

More preferably, the stabilizers of the invention are used to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a peptide metal chelator comprising a single thiol having a formula:

\[
A-\text{CZ(B)-}[C(R'R'')_n]-X
\]

wherein \( A \) is H, HOOC, \( H_2\text{NOC} \), (peptide)-NHOC, (peptide)-OOC or R\text{''''};

wherein \( B \) is H, SH, -NHR\text{''''}, -N(R\text{''''})-(peptide), or R\text{''''};

wherein \( X \) is H, SH, -NHR\text{''''}, -N(R\text{''''})-(peptide) or R\text{''''};

wherein \( Z \) is H or R\text{''''};

wherein \( R', R'', R''' \) and R\text{''''} are independently H or lower straight or branched chain or cyclic alkyl;

where \( n \) is 0, 1 or 2;

and wherein \( B \) is -NHR\text{''''} or -N(R\text{''''})-(peptide), \( X \) is SH, and \( n \) is 1 or 2;

and wherein \( X \) is -NHR\text{''''} or -N(R\text{''''})-(peptide), \( B \) is SH, and \( n \) is 1 or 2;

where \( B \) is H or R\text{''''}, \( A \) is HOOC, \( H_2\text{NOC} \), (peptide)-NHOC, (peptide)-OOC, \( X \) is SH, and \( n \) is 0 or 1;

where \( A \) is H or R\text{''''}, then wherein \( B \) is SH, \( X \) is -NHR\text{''''} or -N(R\text{''''})-(peptide) and wherein \( X \) is SH, \( B \) is -NHR\text{''''} or -N(R\text{''''})-(peptide);

where \( X \) is H or R\text{''''}, \( A \) is HOOC, \( H_2\text{NOC} \), (peptide)-NHOC, (peptide)-OOC and \( B \) is SH;

where \( Z \) is methyl, \( X \) is methyl, \( A \) is HOOC, \( H_2\text{NOC} \), (peptide)-NHOC, (peptide)-OOC, \( B \) is SH and \( n \) is 0.
Such chelators are disclosed and claimed in commonly assigned U.S. Pat. Nos. 5,443,815; 5,807,537; 5,814,297; and 5,866,097.

Specific embodiments of the single thiol containing radiometal chelator stabilized in accordance with the present invention are described and claimed in commonly assigned copending U.S. patent application number 08/236,402 and in WO 95/29708, and include chelators having the chemical formula:

$$\text{R}^1\text{-CO-(amino acid)}^1\text{-(amino acid)}^2\text{-Z}$$

wherein (amino acid)$^1$ and (amino acid)$^2$ are each independently any primary $\alpha$- or $\beta$-amino acid that does not comprise a thiol group, Z is a thiol-containing moiety selected from the group consisting of cysteine, homocysteine, isocysteine, penicillamine, 2-mercaptoethylamine and 3-mercaptopropylamine, and $R^1$ is lower (C$^1$-C$^6$) alkyl, an amino acid, or a peptide comprising 2 to 10 amino acids. When Z is cysteine, homocysteine, isocysteine or penicillamine, the carbonyl group of said moiety is covalently linked to a hydroxyl group, a NR$^3$R$^4$ group, wherein each of R$^3$ and R$^4$ are independently H or lower (C$^1$-C$^4$) alkyl, an amino acid or a peptide comprising 2 to 10 amino acids.

Alternatively, a single thiol containing radiometal chelator stabilized in accordance with the present invention has a formula:

$$\text{Y-(amino acid)}^2\text{- (amino acid)}^1\text{-NH}R^2$$

wherein Y is a thiol-containing moiety that is cysteine, homocysteine, isocysteine, penicillamine, 2-mercaptoacetate or 3-mercaptopropionate, (amino acid)$^1$ and (amino acid)$^2$ are each independently any primary $\alpha$- or $\beta$-amino acid that does not comprise a thiol group, and $R^2$ is H or lower (C$^1$-C$^4$) alkyl, an amino acid or a peptide comprising 2 to 10 amino acids. When Y is cysteine, homocysteine, isocysteine or penicillamine, the amino group of said moiety is covalently linked to $-\text{H}$, an amino acid or a peptide comprising 2 to 10 amino acids.

Specific embodiments of the single thiol containing radiometal chelator are selected from the group consisting of:

$$-(\text{amino acid})^1\text{- (amino acid)}^2\text{-A-CZ(B)-} \{(\text{C}(\text{R}^1\text{R}^2))^n\text{-X}\},$$
$$-\text{A-CZ(B)-} \{(\text{C}(\text{R}^1\text{R}^2))^n\text{-X}\}\text{- (amino acid)}^1\text{- (amino acid)}^2,$$
$$-(\text{a primary }\alpha,\omega\text{- or }\beta,\omega\text{-diamino acid})\text{- (amino acid)}^1\text{-A-CZ(B)-} \{(\text{C}(\text{R}^1\text{R}^2))^n\text{-X}\},$$
and
-A-CZ(B)-{C(R^1R^2)}_n-X\}-(amino acid)^1-(a primary \alpha,\beta- or \alpha,\omega-diamino acid) wherein the term "\alpha,\omega-diamino acid" represents an amino acid having an amine on the \alpha carbon atom and an amine on the carbon atom most distal from the \alpha carbon atom, the term "\beta,\omega-diamino acid" represents an amino acid having an amine on the \beta carbon atom and an amine on the carbon atom most distal from the \beta carbon atom, and (amino acid)^1 and (amino acid)^2 are each independently any naturally-occurring, modified, substituted or altered \alpha- or \beta-amino acid not containing a thiol group.

Specific single thiol-containing radiometal chelators stabilized in accordance with the invention have a formula selected from the group consisting of: -Gly-Gly-Cys-, Cys-Gly-Gly-, -(\varepsilon-Lys)-Gly-Cys-, (\delta-Orn)-Gly-Cys-, -(\gamma-Dab)-Gly-Cys-, -(\beta-Dap)-Lys-Cys-, and -(\beta-Dap)-Gly-Cys-. (In these formulae, \varepsilon-Lys represents a lysine residue in which the \varepsilon-amino group, rather than the typical \alpha-amino group, is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond; \delta-Orn represents an ornithine residue in which the \delta-amino group, rather than the typical \alpha-amino group, is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond; \gamma-Dab represents a 2,4-diaminobutyric acid residue in which the \gamma-amino group is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond; and \beta-Dap represents a 2,3-diaminopropionic acid residue in which the \beta-amino group is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond.)

Most preferably, the stabilizers of the invention may be used to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a monoamine, diamide, single thiol metal chelator such as those disclosed and claimed in commonly assigned copending U.S. patent application serial number 08/253,973 and in WO 95/33497, and to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a bisamide bisthiol metal chelator such as those disclosed and claimed in commonly assigned U.S. Pat. Nos. 5,780,007; 5,922,303; 6,086,849; and 6,093,383. Exemplary monoamine, diamide, single thiol chelators stabilized by a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy chroman have general formulae selected from the group consisting of:

(i)
wherein n, m and p are each integers that are independently 0 or 1; each R' is independently H, lower alkyl, C$_2$-C$_4$ hydroxyalkyl, or C$_2$-C$_4$ alkoxyalkyl, and each R is independently H or R'', where R'' is a substituted lower alkyl group, an unsubstituted lower alkyl group, or a phenyl not comprising a thiol group, and one R or R' is L, where L is a bivalent linker linking the metal chelator to the targeting moiety and wherein when one R' is L, NR''$_2$ is an amine. In preferred embodiments, L is a C$_1$-C$_6$ linear alkyl group; a branched chain alkyl group; a cyclic alkyl group; a carboxylic ester; a carboxamide; a sulfonamide; an ether; a thioether; an amine; an alkene; an alkyne; a 1,2-linked, optionally substituted benzene ring; a 1,3-linked, optionally substituted benzene ring; a 1,4-linked, optionally substituted benzene ring; an amino acid, or a peptide of 2 to about 10 amino acids, or combinations thereof. In preferred embodiments, R'' is a C$_1$-C$_6$ linear alkyl group; a branched alkyl group; a cyclic alkyl group; a -C$_q$OC$_r$-, -C$_q$NHC$_r$- or -C$_q$SC$_r$- group, where q and r are integers each independently 1 to 5 wherein the sum of q + r is not greater than 6; a (C$_1$-C$_6$) alkyl-X, where X is a hydroxyl group; a substituted amine; a guanidine; an amidine; a substituted thiol group; a carboxylic acid; an ester; a phosphate group; a sulfate group; a phenyl group; a phenyl group substituted with a halogen, a hydroxyl, a substituted amine, a guanidine, an
amidine, a substituted thiol, an ether, a phosphate group, or a sulfate group; an indole group; a C₁-C₆ heterocyclic group containing 1 to 3 nitrogen, oxygen or sulfur atoms; or a combination thereof.

In a specific embodiment, the monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may have a formula:

\[
\begin{align*}
&\text{O} \quad \text{NH} \quad \text{HN} \quad \text{O} \\
&R^3 \quad R^6 \\
&R^4 \quad R^7 \quad R^8 \\
&R^9 \quad R^{R^1} R^2 \quad R^7 \\
\end{align*}
\]

wherein \(R^1\) and \(R^2\) are each independently H, lower alkyl, C₂-C₄ hydroxyalkyl, or C₂-C₄ alkoxyalkyl; \(R^3\), \(R^4\), \(R^5\), \(R^6\) are independently H, substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group; \(R^7\) and \(R^8\) are each independently H, lower alkyl, lower hydroxyalkyl or lower alkoxyalkyl; L is a bivalent linker group and Z is a targeting moiety.

The monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may alternatively have a formula:

\[
\begin{align*}
&\text{O} \quad \text{NH} \quad \text{HN} \quad \text{O} \\
&R^5 \quad R^6 \\
&R^3 \quad NR^1 R^2 \quad R^7 \quad R^8 \\
\end{align*}
\]

wherein \(R^1\) and \(R^2\) are each independently H, lower alkyl, C₂-C₄ hydroxyalkyl, or C₂-C₄ alkoxyalkyl; \(R^3\), \(R^4\), \(R^5\) and \(R^6\) are independently H, substituted lower alkyl, unsubstituted lower alkyl, phenyl, substituted phenyl not comprising a thiol group, and one of \(R^3\), \(R^4\), \(R^5\) or \(R^6\) is \(\text{Z-L-HN(\text{CH}_2)_n-}\), where \(L\) is a bivalent linker, \(Z\) is a targeting moiety, and \(n\) is an integer from 1 to 6; \(R^7\) and \(R^8\) are each independently H, lower alkyl, lower hydroxyalkyl, lower alkoxyalkyl; and X is an amino group, a substituted amino group or \(-\text{NR}^1\cdot\text{Y}\), where \(Y\) is an amino acid, an amino acid amide, or a peptide comprising from 2 to 10 amino acids.
The monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may alternatively have a formula:

\[
\begin{align*}
Z &- \text{amide link} - \text{amino group} - \text{thiol group} - R^1 - R^2 \\
&\quad \text{amide link} - \text{amide link} - \text{amide group} - \text{amide group} - X
\end{align*}
\]

wherein \(R^1\) and \(R^2\) are each independently \(H\), lower alkyl, lower hydroxyalkyl, or lower alkenylalkyl; \(R^3\) and \(R^4\) are independently \(H\), substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group; \(n\) is an integer from 1 to 6; \(L\) is a bivalent linker; and \(Z\) is a targeting moiety.

The monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may alternatively have a formula:

\[
\begin{align*}
Z &- \text{amide link} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - X
\end{align*}
\]

wherein \(L\) is a bivalent linker and \(Z\) is a targeting moiety.

Bisamide bisthiol metal chelators stabilized in accordance with the present invention preferably have a formula selected from the group consisting of:

\[
\begin{align*}
\text{CR}_2 &- \text{amide link} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - X \\
&\quad \text{amide link} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - \text{amide group} - X
\end{align*}
\]

wherein
- each \(R\) is independently \(H\), \(\text{CH}_3\) or \(\text{C}_2\text{H}_5\);
- each \((\text{pgp})^s\) is independently a thiol protecting group or \(H\);
m, n and p are independently 2 or 3;
A is linear or cyclic lower alkyl, aryl, heterocyclyl, a combination thereof or a substituted derivative thereof;

and

\[
\begin{align*}
&\text{NH} \quad \text{N=CH(V)NHR'} \\
&(\text{CR}_2)_n \quad (\text{CR}_2)_p \\
&\text{SH} \quad \text{SH}
\end{align*}
\]

wherein each R is independently H, CH₃ or C₂H₅;
m, n and p are independently 2 or 3;
A is linear or cyclic lower alkyl, aryl, heterocyclyl, a combination thereof or a substituted derivative thereof;
V is H or -CO-peptide;
R' is H or peptide;

and wherein when V is H, R' is peptide; and when R' is H, V is -CO-peptide.

For example, the stabilizers of the invention may be used to increase the shelf life of radiopharmaceuticals comprising the specific precursors set forth below:

GGCSIPPEVKFNKPFVYLLamide (SEQ ID NO:1);

GGCSIPPEVKFNKPFVYLI (SEQ ID NO:2);
GGCGLF (SEQ ID NO:3);
RGCSIPPEVKFNKPFVYLLamide (SEQ ID NO:4);
RGCGHRPLDKKREEAPSLRPAPPPISGGYRamide (SEQ ID NO:5);
GGCRPKPQFFGLMamide (SEQ ID NO:6);

GGCFVYLLamide (SEQ ID NO:7);
(acetyl.TKPRGG)₂K(ε-K)GC.amide;
F₁FYW₁KTFT(ε-K)GC.amide;
acetyl.F₁FYW₁KTFT(ε-K)GC.amide;
acetyl.Nal₁.Cpa.YW₁KTFT(ε-K)GCKK.amide;
acetyl.F₁FYW₁KTFTGGG(ε-K)GC.amide;
acetyl.FpFYWDKTFTGGG(ε-K)KC.amide;
acetyl.KKKKK.NalD.Cpa.YWpKTFT(ε-K)GC.amide;
acetyl.DpFrCpA.YWpKTFT(ε-K)GCKK.amide;
acetyl.DpFrCpA.YWpKTC(ε-K)GCKK.amide;
acetyl.KKKKK.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
acetyl.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
acetyl-DDD.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
acetyl.DDpFrCpA.YWpKTFT(ε-K)GCKK.amide;
(DTPA).FrFYWDKTFT(ε-K)GC.amide;
(DTPA).NalD.Cpa.YWDK.T.Nal.T(ε-K)GCKK.amide;
(DTPA).ε-KGCFpFYWDKTFT.amide;
(DTPA).ε-KGCFpCpa.YWpKTFT.amide;
(DTPA).FrCpA.YWpKTFT(ε-K)GC.amide;
(DTPA).NalD.Cpa.YWpKTFT(ε-K)GC.amide;
(DTPA).AcaFrCpA.YWpKTFT(ε-K)GC.amide;
(DTPA).NalD.Cpa.YWDKT.Nal.T(ε-K)GCKK.amide;
(DTPA).NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
CH₂CO.FFWpDKTC(ε-K)GC.amide;
CH₂CO.FFWpDKTFCKKKKK(ε-K)GC.amide;
CH₂CO.FFWpDKTFCKKKKKGC.amide;
AKCGGGFpFYWDKTFT.amide;
AKCGGGFpYWpKTFT.amide;
DDDD.NalD.Cpa.YWpKTFT(ε-K)GCKKKK.amide;
DDDD.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
Trc.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
Heca.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
(Trc)₂.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
KKKK.NalD.Cpa.YWpKTFT(ε-K)GCDDDD.amide;
K<sub>D</sub>.Nal<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCDamide;
K<sub>D</sub>K.K.Nal<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCDDamide;
K<sub>D</sub>KK.K.Nal<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCDDDamide;
K<sub>D</sub>KK.K.Nal<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCDDDamide;
K<sub>D</sub>KKK.K.Nal<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCDDDamide;
K<sub>D</sub>KKK.K.Nal<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCDDDamide;
K<sub>D</sub>KK.F.D.Cpa.YW<sub>D</sub>KTFT.Nal.(ε-K)GCDDD.Damide;
K.BAT.Nal.D.CMeYW<sub>D</sub>KVCMe.Tamide
K<sub>D</sub>D.KD.D.Nal.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCKDKDamide;
KDKD.Nal.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCKDKDamide;
F<sub>D</sub>.Cpa.YW<sub>D</sub>KTC(ε-K)GCKKamide;
F<sub>D</sub>.Cpa.YW<sub>D</sub>KTC(ε-K)GCamide;
F<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCKKamide;
F<sub>D</sub>.Cpa.YW<sub>D</sub>KTFTGGG(ε-K)GCamide;
F<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCRamide;
(Trc-imide).Nal.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCRamide;
Trc.(Trc-imide).K.Nal.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCRRamide;
(Trc-imide)<sub>2</sub>.K.Nal.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCRRamide;
(Trc-imide)<sub>2</sub>.K.Nal.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCRamide;
D<sub>D</sub>DF.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCKKamide;
D<sub>D</sub>DF.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCKKamide;
F<sub>D</sub>FY<sub>D</sub>KTFT(ε-K)GCKKamide;
AKCG.GGF.DYW<sub>D</sub>KTFTamide;
(2-ketogulonyl).Nal.D.Cpa.YW<sub>D</sub>KTFT(ε-K)GCKKamide;
(2-ketogulonyl).F<sub>D</sub>.Cpa.YW<sub>D</sub>KTFT(ε-K)GCamide;
cyclo-(N-CH<sub>3</sub>)FY<sub>D</sub>KV.Hcy(CH<sub>3</sub>CO.GC.Dap.Dapamide);
cyclo-(N-CH<sub>3</sub>)FY<sub>D</sub>KV.Hcy(CH<sub>3</sub>CO.(γ-Dap)KCRamide);
cyclo-(N-CH<sub>3</sub>)FY<sub>D</sub>KV.Hcy(CH<sub>3</sub>CO.KKKKK(ε-K)GCamide);
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).((ė-K)GCK.amide);
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).((β-Dap)KCR.amide);
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).((β-Dap)KCK.amide);
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).((δ-Om)GCK.amide);
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).((β-Dap)GCK.amide);
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).K(ė-K)KCK.amide;
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).K(ė-K)GCK.amide;
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).K(ė-K)GC.amide;
cyclo-(N-CH₃)FYWDKV.Hcy(CH₃CO).K(ė-K)GC.amide;

RGCQAPLYKIIKLLLES (SEQ ID NO:8);
acetyl.KK(ė-K)GCGCGPPLYKIIKLLLES;
acetyl.KKKK.KK(ė-K)GCGGFPALLYKIIKLLLES;
(CH₃CO.YD.Apc.GDCKGCG.amide)₂(CH₃CO)₂K(ė-K)GC.amide;
(CH₃CO.YD.Apc.GDCGGCG(CG-Am)GCG amat)₂(CH₃CO)₂K(ė-K)GC.amide;

(Ch₃CO.YD.Apc.GDCKGCG.amide)₂(CH₃CO)₂K(ė-K)GC.amide;
{(Ch₃CO.YD.Apc.GDCKGCG.amide)(Ch₃CO)}₂K(ė-K)GC.amide;
(Ch₃CO.YD.Apc.GDCKGCG)₂K(ė-K)GC.β-Ala.amide;
(Ch₃CO.YD.Apc.GDCKGKG)₂K(ė-K)GC.β-Ala.amide;
{(Ch₃CO.YD.Apc.GDCKGKG)₂K(ė-K)GC.amide;

(HSDAVFTDNYTRLKQMAVKKYLNSILN(ė-K)GC.amide;
HSDAVFTDNYTRLKQMAVKKYLNSILN.GCG.amide (SEQ ID NO:9);
AGCHSDAVFTDNYTRLKQMAVKKYLNSILN.amide (SEQ ID NO:10);
HSDAVFTDNYTRLKQMAVKKYLNSILN.C(BAT).amide (SEQ ID NO:11);
CH₃CO.SNLST.HhcVLGKLSG(BAT)ELHKLQTYPRNTNGTSGTP.amide (SEQ ID NO:12);
CH₃CO.SNLST.HhcVLGKLSQELHKLQTYPRNTNGTSGTP(ė-K)GC.amide;
CH₂CO.SNLST.HheVGLKSLC(CH₂CO.GGCK.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.HheVGLKSLC(CH₂CO.(β-Dap)KCK.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.HheVGLKSLC(CH₂CO.(ε-K)GCE.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.HeyVGLKSLC(CH₂CO.GGCK.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.HeyVGLKSLC(CH₂CO.(β-Dap)KCK.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.HeyVGLKSLC(CH₂CO.(ε-K)GCE.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.Cys.LGKSLC(CH₂CO.GGCK.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.CysVGLKSLC(CH₂CO.(β-Dap)KCK.amide)ELHKLQTPRNTGSOTP.amide;
CH₂CO.SNLST.CysVGLKSLC(CH₂CO.(ε-K)GCE.amide)ELHKLQTPRNTGSOTP.amide;

SNLST.AsuVGLKSLC(CH₂CO.(β-Dap)KCK.amide)ELHKLQTPRNTGSOTP.amide;
SNLST.AsuVGLKSLC(CH₂CO.(β-Dap)KCK.amide)ELHKLQTPRDVGAGTP.amide;
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Tyr-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Phe(4-F)-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Phe(4-NH₂)-Cys-Thr-Ser);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Dab-Cys-Thr);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Phe(4-NH₂)-Cys-Thr);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Phe(4-NH₂)-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-His-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Ag-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Gly-Cys-Lys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Ser-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Dab-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Gly-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Dab-Cys-Ser(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-Lys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-Arg-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Lys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Arg-NH₃);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Lys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Dap-NH₃);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-
NH(CH₂CH₂O)₂CH₂CH₂NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy
(CH₂CO-β-Dap-Ser-Cys-Thr-NH(CH₂CH₂O)₂CH₂CH₂NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Lys-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Lys-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Lys-Gly-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Dab-Cys-Ser(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Dap-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-His-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-Phe(4-NH₂)-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Orn-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Dap-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Lys-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-NHCH₂CH₂OCH₂CH₂NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Lys-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Omn-Gly-Gly-Cys-NH₂); and

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Thr-Gly-Gly-Cys-NH₂).

(Single-letter and three-letter abbreviations for amino acids can be found in G. Zubay, *Biochemistry* (2d. ed.), 1988 (MacMillan Publishing: New York) p.33; other abbreviations are as follows: Acm is acetamidomethyl; Mob is 4-methoxybenzyl; Abu is aminobutyric acid; F_D is D-phenylalanine; W_D is D-tryptophan; Y_D is D-tyrosine; Aca is 6-aminohexanoic acid; Apc is S-(3-aminopropyl)cysteine; Hcy is homocysteine; Nal is 2-naphthylalanine; Cpa is 4-chlorophenylalanine; K_D is D-lysine; D_D is D-aspartate; NalD is D-2-naphthylalanine; DTPA is diethylenetriaminepentaacetic acid; Trc is tricarballylic acid; Trc-imide is tricarballylic imide; and Hca is hexacarboxycyclohexane. (...)₂K represents covalent linkage to both amino groups of lysine. Hcy(...) represents covalent linkage to the
sidechain sulfur atom of homocysteine. (N-CH₃)F represents N-α-methyl-phenylalanine. Underlining between groups (e.g., as between the CH₂CO. group and cysteine (C) in CH₂CO.Y₆RGDC) represents a cyclic sulfide. Underlining between amino acids (e.g., as between the cysteines (C) in CNPRGDC) represents a cyclic disulfide bond. The term "cyclo" before an underlined sequence means an N-terminus-to-C-terminus cyclic sequence. The subscript X₆ indicates the amino acid is in the d-configuration; all other subscripts refer to amino acid sidechain protecting groups. ε-K, δ-Orn, γ-Dab, and β-Dap are defined as set forth above. Asu is 2-amino suberic acid, wherein the amino terminal amino acids of peptides containing an Asu residue are cyclized via an amide bond between the amino terminal amino group and the side chain carboxylic acid moiety of the Asu residue. BAT is N⁶, N²¹-bis(2-mercapto-2-methylpropyl)-6,9-diazanonanoic acid.

In accordance with the present invention, a hydrophilic 6-hydroxy-chroman derivative may also be used to stabilize labelled radiopharmaceutical precursors comprising a benzodiazepine derivative, such as those described in U.S.Pat.No. 6,171,578. In a preferred embodiment, a hydrophilic 6-hydroxy-chroman derivative such as 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid is used to stabilize radiolabelled 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-aminophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate.

In addition, a hydrophilic thioether, or hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxychroman derivative may be used in accordance with the present invention to stabilize labelled radiopharmaceutical precursors comprising a targeting moiety or domain covalently linked to the known chelators 1,4,7,10-tetraazadodecanetetraacetic acid and derivatives thereof:
where n is an integer that is 2 or 3 and where each R is independently H, C₁ to C₄ alkyl, or aryl and one R is covalently linked to the targeting moiety, and desferrioxamine.

A radiopharmaceutical comprising any radionuclide or radiometal may be stabilized in accordance with the present invention. For example, radiopharmaceuticals containing such nuclides as $^{125}$I, $^{131}$I, $^{211}$At, $^{67}$Sc, $^{68}$Ga, $^{72}$Ga, $^{90}$Y, $^{153}$Sm, $^{159}$Gd, $^{165}$Dy, $^{166}$Ho, $^{175}$Yb, $^{177}$Lu, $^{186}$Re, $^{188}$Re, $^{212}$Bi, $^{213}$Bi, $^{68}$Ga, $^{99m}$Tc, $^{111}$In, and $^{123}$I, and the like may be stabilized by addition of a hydrophilic thioether in accordance with the invention. The extent of stabilization of a particular radiopharmaceutical precursor when chelated to different radionuclides may vary. For example, a $^{99m}$Tc-labelled precursor may be stabilized to a greater extent than a $^{188}$Re-labelled form of the same precursor.

The compositions of the invention are formulated as a sterile, pyrogen-free, parenterally acceptable aqueous solution which may optionally be supplied in lyophilized form and be reconstituted by the user. The compositions of the invention may be provided as components of kits which may include buffers, additional vials, instructions for use, and the like.

The pharmaceutical compositions of the invention comprise a radiopharmaceutical precursor in combination with a stabilizing amount of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and hydrophilic 6-hydroxy-chroman, optionally with a pharmaceutically acceptable diluent or a carrier such as species appropriate albumin. As used herein, a “pharmaceutically acceptable diluent or carrier” may include any and all solvents, dispersion media, antibacterial and antifungal agents, isotonic agents, enzyme inhibitors, transfer ligands such as glucoheptonate, tartrate, citrate, or mannitol, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. For example, Sodium Chloride Injection and Ringer’s Injection are commonly used as diluents. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art.

In accordance with the method of this invention, radiopharmaceuticals are preferably administered intravenously in a single unit dose, either totally as a bolus or partly as a bolus followed by infusion over 1-2 hours. The amount of solution to be injected at unit dosage is from about 0.01 mL to about 10 mL, containing about 0.01 mCi to about 100 mCi of
radioactivity, preferably from about 1 mCi to about 50 mCi. The amount of the radiopharmaceutical in the unit dose may range from about 0.1 to about 10 mg/kg body weight. After intravenous administration, the site is monitored, for example, by radioimaging in vivo if the radiopharmaceutical is a diagnostic agent.

The following examples are shown by way of illustration and not be considered as limitations.

**EXAMPLE 1**

**Effect of Gentisic Acid on Radiochemical Purity of $^{99m}$Tc-labelled Depreotide**

Gentisic acid (GA) was tested for its ability to stabilize the $^{99m}$Tc-labelled somatostatin receptor-binding peptide depreotide, which has the structure.

![Structural formula of depreotide](image)

This peptide is represented as:

$$cyclo(N-\text{CH}_3)FYW_DKVK.Hcy.(\text{CH}_2\text{CO.(β-Dap)KCKamide})$$

in the listing set forth above.

Lyophilized kit vials were prepared containing depreotide, GA, and other components as described in Table 1. Formulations were adjusted to pH 7.4 or 8.5 (as noted) prior to lyophilization.

**TABLE 1**

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>GA I</th>
<th>GA II</th>
<th>GA III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depreotide</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>Sodium Glucoheptonate Dihydrate(^1)</td>
<td>25 mg</td>
<td>25 mg</td>
<td>5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Edetate Disodium Dihydrate(^2)</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
</tr>
<tr>
<td>Stannous Chloride Dihydrate(^3)</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
</tbody>
</table>
The lyophilized kits were radiolabelled with $^{99m}$Tc by reconstitution with 1.0 mL technetium $^{99m}$Tc sodium pertechnetate (Technelite® Molybdenum Mo99-Technetium Tc99m Generator, DuPont, Billerica, Massachusetts) containing approximately 50 mCi $^{99m}$Tc and heating in a boiling water bath for 10 minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 2.

**TABLE 2**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>94.5</td>
<td>88.3</td>
<td>86.4</td>
</tr>
<tr>
<td></td>
<td>94.2</td>
<td>92.1</td>
<td>90.8</td>
</tr>
<tr>
<td></td>
<td>94.5</td>
<td>91.7</td>
<td>90.1</td>
</tr>
<tr>
<td>(Average ± 1SD):</td>
<td>(94.4 ± 0.2)</td>
<td>(90.7 ± 2.1)</td>
<td>(89.1 ± 2.4)</td>
</tr>
<tr>
<td>GA I</td>
<td>82.4</td>
<td>79.4</td>
<td>77.2</td>
</tr>
<tr>
<td>GA II</td>
<td>29.1</td>
<td>25.1</td>
<td>20.5</td>
</tr>
<tr>
<td>GA III</td>
<td>0.9</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

These results indicate that gentisic acid decreases the radiolabelling yield and the stability of $^{99m}$Tc-depreotide when included in formulated kits.

**EXAMPLE 2**

Stabilization of $^{99m}$Tc-labelled Depreotide by L-Methionine

Lyophilized kit vials were prepared containing depreotide, L-methionine (Met), and other components as described in Table 3. All formulations were adjusted to pH 7.4 prior to lyophilization.

**TABLE 3**

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Met I</th>
<th>Met II</th>
<th>Met III</th>
<th>Met IV</th>
<th>Met V</th>
</tr>
</thead>
</table>
The lyophilized kits were radiolabelled with $^{99m}Tc$ by reconstitution with 1.0 mL technetium $^{99m}Tc$ sodium pertechnetate (Technelite®) containing approximately 50 mCi $^{99m}Tc$ and heating in a boiling water bath for 10 minutes. Some of the formulations were also radiolabelled in a room temperature preparation (allowed to stand at room temperature 30 minutes following reconstitution). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 4.

**TABLE 4**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Prep Type</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Heated</td>
<td>91.9</td>
<td>85.0</td>
<td>80.7</td>
</tr>
<tr>
<td></td>
<td>Heated</td>
<td>91.9</td>
<td>81.6</td>
<td>79.3</td>
</tr>
<tr>
<td></td>
<td>(Average):</td>
<td>(91.9)</td>
<td>(83.3)</td>
<td>(80.0)</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>94.8</td>
<td>87.6</td>
<td>78.2</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>90.7</td>
<td>88.7</td>
<td>83.4</td>
</tr>
<tr>
<td></td>
<td>(Average):</td>
<td>(92.8)</td>
<td>(88.2)</td>
<td>(80.8)</td>
</tr>
<tr>
<td>Met I (1 mg)</td>
<td>Heated</td>
<td>95.9</td>
<td>91.5</td>
<td>89.5</td>
</tr>
<tr>
<td>Met II (2 mg)</td>
<td>Heated</td>
<td>95.2</td>
<td>93.2</td>
<td>90.5</td>
</tr>
<tr>
<td>Met III (4 mg)</td>
<td>Heated</td>
<td>95.9</td>
<td>93.5</td>
<td>92.2</td>
</tr>
<tr>
<td></td>
<td>Heated</td>
<td>92.4</td>
<td>88.5</td>
<td>87.4</td>
</tr>
<tr>
<td></td>
<td>(Average):</td>
<td>(94.2)</td>
<td>(91.0)</td>
<td>(89.8)</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>90.4</td>
<td>90.0</td>
<td>89.4</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>89.9</td>
<td>89.9</td>
<td>89.7</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>91.4</td>
<td>87.9</td>
<td>83.1</td>
</tr>
<tr>
<td></td>
<td>(Average ± 1SD):</td>
<td>(90.6 ± 0.8)</td>
<td>(89.3 ± 1.2)</td>
<td>(87.4 ± 3.7)</td>
</tr>
<tr>
<td>Met IV (5 mg)</td>
<td>Heated</td>
<td>93.8</td>
<td>93.7</td>
<td>93.5</td>
</tr>
<tr>
<td></td>
<td>Heated</td>
<td>-</td>
<td>92.5</td>
<td>92.7</td>
</tr>
<tr>
<td></td>
<td>(Average):</td>
<td>(93.8)</td>
<td>(93.1)</td>
<td>(93.1)</td>
</tr>
<tr>
<td>Met V (10 mg)</td>
<td>Heated</td>
<td>94.5</td>
<td>94.6</td>
<td>92.6</td>
</tr>
</tbody>
</table>
These results indicate that L-methionine increases the radiolabelling yield and the stability of $^{99m}$Tc-deproetide prepared from formulated kits which have been stored under normal conditions ($\leq -10^\circ C$).

**EXAMPLE 3**

**Stabilization of $^{99m}$Tc-labelled Deprotide by L-Methionine in Lyophilized Kit Preparations; Accelerated Temperature (40$^\circ$C) Storage**

Lyophilized kits were prepared containing deproetide, L-methionine (Met), and other components as described in Table 5. All formulations were adjusted to pH 7.4 prior to lyophilization. The kits were stored for one week at 40$^\circ$C. Some kits were also stored at -10$^\circ$C as controls.

**TABLE 5**

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deprotide</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>Sodium Glucoheptonate Dihydrate</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>EDTA Disodium Dihydrate</td>
<td>100 µg</td>
<td>100 µg</td>
</tr>
<tr>
<td>Stannous Chloride Dihydrate</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>L-Methionine USP</td>
<td>-</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

The lyophilized kits were radiolabelled with $^{99m}$Tc by reconstitution with 1.0 mL technetium $^{99m}$Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi $^{99m}$Tc and incubation in a boiling water bath (10 min). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 6.

**TABLE 6**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Storage Temp</th>
<th>Prep Type</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-10$^\circ$C</td>
<td>Heated</td>
<td>-</td>
<td>82.6</td>
<td>77.8</td>
</tr>
<tr>
<td></td>
<td>40$^\circ$C</td>
<td>Heated</td>
<td>-</td>
<td>82.6</td>
<td>79.0</td>
</tr>
<tr>
<td>Met</td>
<td>40$^\circ$C</td>
<td>Heated</td>
<td>76.5</td>
<td>78.0</td>
<td>77.6</td>
</tr>
</tbody>
</table>
These results indicate that L-methionine does not stabilize $^{99m}$Tc-depreotide in lyophilized kits which have been stored at 40°C prior to radiolabelling.
EXAMPLE 4

Stabilization of $^{99m}$Tc-labelled Benzodiazepinedione Derivative by L-Methionine in Lyophilized Kit Preparations

L-methionine was tested for its ability to stabilize a $^{99m}$Tc-labelled glycoprotein IIb/IIIa receptor-binding benzodiazepinedione derivative 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxylethyl)-7-[(4-aminophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate, having the structure.

Lyophilized kit vials were prepared containing the benzodiazepinedione derivative and components as described in Table 7. All formulations were adjusted to pH 7.4 prior to lyophilization.

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivative</td>
<td>40 µg</td>
<td>40 µg</td>
</tr>
<tr>
<td>Sodium Glucoheptonate Dihydrate</td>
<td>25 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Edetate Disodium Dihydrate</td>
<td>100 µg</td>
<td>100 µg</td>
</tr>
<tr>
<td>Stannous Chloride Dihydrate</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>L-Methionine USP</td>
<td>-</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

The lyophilized kits were radiolabelled with $^{99m}$Tc by reconstitution with 1.0 mL technetium $^{99m}$Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi
$^{99m}$Tc and heating in a boiling water bath for 10 minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 8.

### TABLE 8

<table>
<thead>
<tr>
<th>Formulation</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>93.2</td>
<td>90.1</td>
<td>88.0</td>
</tr>
<tr>
<td></td>
<td>93.6</td>
<td>94.5</td>
<td>88.8</td>
</tr>
<tr>
<td></td>
<td>92.4</td>
<td>89.2</td>
<td>88.1</td>
</tr>
<tr>
<td></td>
<td>85.0</td>
<td>86.1</td>
<td>82.3</td>
</tr>
<tr>
<td>(Average ± 1SD):</td>
<td>(91.0 ± 4.1)</td>
<td>(90.0 ± 3.5)</td>
<td>(86.8 ± 3.0)</td>
</tr>
<tr>
<td>Met (5 mg)</td>
<td>92.5</td>
<td>91.1</td>
<td>91.4</td>
</tr>
<tr>
<td></td>
<td>93.9</td>
<td>92.5</td>
<td>91.9</td>
</tr>
<tr>
<td></td>
<td>94.3</td>
<td>92.4</td>
<td>91.0</td>
</tr>
<tr>
<td></td>
<td>90.5</td>
<td>91.2</td>
<td>91.9</td>
</tr>
<tr>
<td>(Average ± 1SD):</td>
<td>(92.8 ± 1.7)</td>
<td>(91.8 ± 0.8)</td>
<td>(91.6 ± 0.4)</td>
</tr>
</tbody>
</table>

These results indicate that L-methionine increases the radiolabelling yield and the stability of the $^{99m}$Tc-labelled benzodiazepinedione derivative prepared from formulated kits.

### EXAMPLE 5

**Stabilization of Tc 99m-labelled Peptide by L-Methionine**

L-methionine was tested for its ability to stabilize a $^{99m}$Tc-labelled glycoprotein IIb/IIIa receptor-binding peptide having the structure.

![Peptide Structure]

This peptide is represented as:

$$(\text{CH}_3\text{CO} \cdot Y_{D} \cdot \text{Amp} \cdot \text{GDC} \cdot \text{KGCG.amide})_2(\text{CH}_3\text{CO})_2K(\varepsilon-K)\text{GC.amide}$$

in the listing set forth above.
Lyophilized kit vials were prepared containing the peptide (50 μg), sodium glucoheptonate dihydrate (10 mg), stannous chloride dihydrate (50 μg), and edetate disodium dihydrate (100 μg). The formulation was adjusted to pH 7.4 prior to lyophilization.

The lyophilized kits were radiolabelled with $^{99m}$Tc in the presence and absence of L-methionine. To the Met preparation was added 4 mg methionine (in 100 μL saline) and 100 μL ethanol. To the control preparation was added 100 μL ethanol and 100 μL saline to account for the additional saline or ethanol added with the L-methionine. Both vials were then reconstituted with 1.0 mL technetium $^{99m}$Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi $^{99m}$Tc and allowed to incubate for 30 minutes at room temperature. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 9.

### TABLE 9

<table>
<thead>
<tr>
<th>Preparation</th>
<th>HPLC RCP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 hr</td>
</tr>
<tr>
<td>Control</td>
<td>91.8</td>
</tr>
<tr>
<td>Methionine (4 mg)</td>
<td>96.7</td>
</tr>
</tbody>
</table>

These results show that L-methionine increases the radiolabelling yield and the stability of the $^{99m}$Tc-peptide.

**EXAMPLE 6**

**Stabilization of $^{99m}$Tc-labelled Peptide Chelator by L-Methionine**

L-methionine was tested for its ability to stabilize a $^{99m}$Tc-labelled monoamine, diamide, single thiol peptide chelator having the structure.

![Chemical Structure](image-url)
N-3-benzoyl-2,3-(S)-diaminopropionyl-L-lysiny1-L-cysteinyl-L-lysiny1 amide

Lyophilized kit "placebo" vials were prepared containing sodium glucoheptonate dihydrate, edetate disodium dihydrate, and stannous chloride dihydrate at the concentrations set forth in Table 1 (control formulation).

The peptide chelator was radiolabelled with $^{99m}$Tc in the presence and absence of L-methionine. The peptide chelator was dissolved in water at a concentration of 1 mg/mL, and 50 μg (50 μL) of the peptide was added to each of three placebo vials. Ethanol and L-methionine were added to the control and methionine preparations as described in Example 5. In addition, 100 μL phosphate buffered saline (PBS) was added to each preparation. The vials were reconstituted with 0.9-1.0 mL $^{99m}$Tc sodium pertechnetate (Technelte®) containing approximately 50 mCi $^{99m}$Tc, and heated in a boiling water bath for ten minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 10.

**TABLE 10**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>HPLC RCP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 hr</td>
</tr>
<tr>
<td>Control</td>
<td>94.1</td>
</tr>
<tr>
<td>L-Methionine (4 mg)</td>
<td>98.4</td>
</tr>
</tbody>
</table>

These results show that L-methionine increases the radiolabelling yield and the stability of a $^{99m}$Tc-labelled peptide chelator.

**EXAMPLE 7**

**Stabilization of a $^{99m}$Tc Bisamine Bisthiol Chelator by L-Methionine**

L-methionine was tested for its ability to stabilize a $^{99m}$Tc-labelled non-peptide chelator (4-(butanoic acid)-2,2,9,9 tetramethyl-4,7-diaza-1,10-decanedithiol) having the structure.
The non-peptide chelator was radiolabelled with $^{99m}$Tc in the presence and absence of L-methionine using the placebo vial heated preparation procedure as described in Example 6. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 11.

**TABLE 11**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>0.5 hr</th>
<th>3 hr</th>
<th>6 hr</th>
<th>9 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>48.5</td>
<td>56.5</td>
<td>54.0</td>
<td>52.9</td>
</tr>
<tr>
<td>Methionine (4 mg)</td>
<td>66.7</td>
<td>70.0</td>
<td>70.8</td>
<td>70.4</td>
</tr>
</tbody>
</table>

These results show that L-methionine increases the radiolabelling yield and the stability of a $^{99m}$Tc-labelled non-peptide chelator.

**EXAMPLE 8**

Stabilization of a $^{99m}$Tc-labelled Peptide by Methionine Derivatives

2-(Ethylthio)ethylamine, methioninol, and 3-methylthio-1,2-propanediol are hydrophilic thioethers having the structures.

- Methionine
- 2-(Ethylthio)ethylamine
- Methioninol
- 3-Methylthio-1,2-propanediol
These compounds and L-methionine were tested for their ability to stabilize $^{99m}$Tc-labelled depreotide.

Each hydrophilic thioether was dissolved in water made up at 40 mg/mL and adjusted to pH 7 with HCl or NaOH. Each hydrophilic thioether (4 mg in 100 μL) was added to a formulated kit vial containing the peptide (“control” formulation in Table 1). To the control vials were added 100 μL water. The vials were reconstituted with 1.0 mL $^{99m}$Tc sodium pertechnetate (Technelit®) containing approximately 50 mCi $^{99m}$Tc and heated in a boiling water bath for ten minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 12.

<table>
<thead>
<tr>
<th>Additive</th>
<th>Initial RCP</th>
<th>3.5 hr RCP</th>
<th>6.5 hr RCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (Control 1)</td>
<td>89.8</td>
<td>82.9</td>
<td>79.4</td>
</tr>
<tr>
<td>Methionine</td>
<td>95.0</td>
<td>90.4</td>
<td>89.3</td>
</tr>
<tr>
<td>2-(Ethylthio)ethylamine</td>
<td>92.8</td>
<td>94.2</td>
<td>93.3</td>
</tr>
<tr>
<td>Day 2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (Control 2)</td>
<td>89.9</td>
<td>78.0</td>
<td>74.4</td>
</tr>
<tr>
<td>Methioninol</td>
<td>94.1</td>
<td>93.9</td>
<td>90.7</td>
</tr>
<tr>
<td>3-Methylthio-1,2-propanediol</td>
<td>89.1</td>
<td>84.0</td>
<td>80.9</td>
</tr>
</tbody>
</table>

These results show that the hydrophilic thioethers 2-(ethylthio)ethylamine, methioninol, and 3-methylthio-1,2-propanediol increase the radiolabelling yield and the stability of a $^{99m}$Tc-labelled peptide. Methionine sulfoxide, methionine sulfone, and 3-(methylthio)propionaldehyde had no effect on $^{99m}$Tc-labelled peptide radiolabelling yield or stability.
EXAMPLE 9

Stabilization of 99mTc-labelled Depreotide by Trolox®

Lyophilized kit vials were prepared containing depreotide, Trolox®, and other components as described in Table 13. All formulations were adjusted to pH 7.4 prior to lyophilization.

**TABLE 13**

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Trolox I</th>
<th>Trolox II</th>
<th>Trolox III</th>
<th>Trolox IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depreotide</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>Sodium Glucoheptonate Dihydrate</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Disodium Dihydrate</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
</tr>
<tr>
<td>Stannous Chloride Dihydrate</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>Trolox</td>
<td>-</td>
<td>0.6 mg</td>
<td>1 mg</td>
<td>2 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The lyophilized kits were radiolabelled with 99mTc by reconstitution with 1.0 mL technetium 99mTc sodium pertechnetate (Technelite®) containing approximately 50 mCi 99mTc and incubation at room temperature for 30 minutes following reconstitution. Some of the formulations were also radiolabelled in a heated preparation (heat in a boiling water bath for 10 minutes). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 14.
Table 14

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Prep Type</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Heated</td>
<td>92.0</td>
<td>85.9</td>
<td>84.5</td>
</tr>
<tr>
<td></td>
<td>Heated</td>
<td>91.4</td>
<td>85.3</td>
<td>78.3</td>
</tr>
<tr>
<td></td>
<td>(Average)</td>
<td>(91.7)</td>
<td>(85.6)</td>
<td>(81.5)</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>92.0</td>
<td>85.0</td>
<td>84.2</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>92.6</td>
<td>85.2</td>
<td>80.7</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>92.0</td>
<td>81.4</td>
<td>79.5</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>89.5</td>
<td>82.8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(Average ± 1SD)</td>
<td>(91.5 ± 1.4)</td>
<td>(83.6 ± 1.8)</td>
<td>(81.5 ± 2.4)</td>
</tr>
<tr>
<td>Trolox I (600 µg)</td>
<td>Rm Temp</td>
<td>94.3</td>
<td>93.2</td>
<td>92.0</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>91.8</td>
<td>88.6</td>
<td>89.1</td>
</tr>
<tr>
<td></td>
<td>(Average)</td>
<td>(93.1)</td>
<td>(90.9)</td>
<td>(90.6)</td>
</tr>
<tr>
<td>Trolox II (1 mg)</td>
<td>Rm Temp</td>
<td>91.3</td>
<td>89.6</td>
<td>91.0</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>92.9</td>
<td>91.8</td>
<td>92.5</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>94.1</td>
<td>93.2</td>
<td>91.1</td>
</tr>
<tr>
<td></td>
<td>(Average ± 1SD)</td>
<td>(92.8 ± 1.4)</td>
<td>(91.5 ± 1.8)</td>
<td>(91.5 ± 0.8)</td>
</tr>
<tr>
<td>Trolox III (2 mg)</td>
<td>Heated</td>
<td>94.9</td>
<td>91.1</td>
<td>85.6</td>
</tr>
<tr>
<td></td>
<td>Heated</td>
<td>95.3</td>
<td>92.9</td>
<td>88.7</td>
</tr>
<tr>
<td></td>
<td>(Average)</td>
<td>(95.1)</td>
<td>(92.0)</td>
<td>(87.2)</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>95.4</td>
<td>94.8</td>
<td>95.4</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>94.5</td>
<td>93.7</td>
<td>93.8</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>95.5</td>
<td>-</td>
<td>92.2</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>93.8</td>
<td>91.7</td>
<td>92.4</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>94.8</td>
<td>92.4</td>
<td>93.0</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>-</td>
<td>94.6</td>
<td>93.5</td>
</tr>
<tr>
<td></td>
<td>(Average ± 1SD)</td>
<td>(94.8 ± 0.7)</td>
<td>(93.4 ± 1.4)</td>
<td>(93.4 ± 1.2)</td>
</tr>
<tr>
<td>Trolox IV (5 mg)</td>
<td>Rm Temp</td>
<td>93.3</td>
<td>92.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>92.1</td>
<td>94.8</td>
<td>93.8</td>
</tr>
<tr>
<td></td>
<td>(Average)</td>
<td>(92.7)</td>
<td>(93.4)</td>
<td>(93.8)</td>
</tr>
</tbody>
</table>

These results indicate that Trolox® increases the radiolabelling yield and the stability of $^{99m}$Tc depretide prepared from formulated kits.
EXAMPLE 10

Stabilization of $^{99m}$Tc Depreotide by Trolox® in Lyophilized Kit Preparations;
Accelerated Temperature (40°C) Storage

Lyophilized kits were prepared containing depreotide, Trolox®, and other components as
described in Table 15. All formulations were adjusted to pH 7.4 prior to lyophilization.
The kits were stored for one week at 40°C. Some kits were also stored at -10°C as
controls.

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Trolox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depreotide</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>Sodium Gluconate Dihydrate</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Edetate Disodium Dihydrate</td>
<td>100 µg</td>
<td>100 µg</td>
</tr>
<tr>
<td>Stannous Chloride Dihydrate</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
</tbody>
</table>

The lyophilized kits were radiolabelled with $^{99m}$Tc by reconstitution with 1.0 mL
technetium $^{99m}$Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi
$^{99m}$Tc and incubation either at room temperature (30 minutes) or in a boiling water bath
(10 min). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are
given in Table 16.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Storage Temp</th>
<th>Prep Type</th>
<th>HPLC RCP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-10°C</td>
<td>Heated</td>
<td>0.5 hr</td>
</tr>
<tr>
<td>Control</td>
<td>40°C</td>
<td>Heated</td>
<td>82.6</td>
</tr>
<tr>
<td>Trolox®</td>
<td>-10°C</td>
<td>Rm Temp</td>
<td>94.4</td>
</tr>
<tr>
<td></td>
<td>40°C</td>
<td>Rm Temp</td>
<td>86.6</td>
</tr>
</tbody>
</table>

These results indicate that the Trolox® stabilizes $^{99m}$Tc-depreotide prepared from
lyophilized kits which had been thermally stressed under conditions of accelerated
temperature storage.
EXAMPLE 11

Stabilization of a $^{99m}$Tc -labelled Peptide by Trolox

Trolox® was tested for its ability to stabilize a $^{99m}$Tc-labelled glycoprotein IIb/IIIa receptor-binding peptide having the structure.

![Peptide Structure](image)

This peptide is represented as:

$\text{(CH}_2\text{CO})_2\text{YD-Amp-GDC,KGCG.amide)}_2\text{(CH}_2\text{CO})_2\text{K(e-K)GC.amide}$

in the listing set forth above.

Lyophilized kit vials were prepared containing the peptide (50 μg), sodium glucoheptonate dihydrate (10 mg), stannous chloride dihydrate (50 μg), and edetate disodium dihydrate (100 μg). The formulation was adjusted to pH 7.4 prior to lyophilization.

The lyophilized kits were radiolabelled with $^{99m}$Tc in the presence and absence of Trolox®. To the Trolox® preparation was added 2 mg Trolox® in 100 μL ethanol and 100 μL saline. The ethanol was necessary to aid in the dissolution of the Trolox®. To the control preparation was added 100 μL ethanol and 100 μL saline to account for the additional saline or ethanol added with the Trolox. Both vials were then reconstituted with 1.0 mL technetium $^{99m}$Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi $^{99m}$Tc and allowed to incubate for 30 minutes at room temperature. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 17.
TABLE 17

<table>
<thead>
<tr>
<th>Preparation</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>91.8</td>
<td>80.4</td>
<td>76.2</td>
</tr>
<tr>
<td>Trolox® (2 mg)</td>
<td>89.5</td>
<td>91.9</td>
<td>92.9</td>
</tr>
</tbody>
</table>

These results show that Trolox® increases the radiolabelling yield and the stability of \( {^{99m}Tc} \)-peptide.

EXAMPLE 12

Stabilization of \( {^{99m}Tc} \)-labelled Peptide Chelator by Trolox®

Trolox® was tested for its ability to stabilize a \( {^{99m}Tc} \)-labelled monoamine, diamide, single thiol peptide chelator having the structure.

\[
\text{N}-3\text{-benzoyl-2,3-(S)-diaminopropionyl-L-lysinyll-L-cysteynil-L-lysinyll amide}
\]

Lyophilized kit “placebo” vials were prepared containing sodium glucoheptonate dihydrate, edetate disodium dihydrate, and stannous chloride dihydrate at the concentrations set forth in Table 1 (control formulation).

The peptide chelator was radiolabelled with \( {^{99m}Tc} \) in the presence and absence of Trolox®. The peptide chelator was dissolved in water at a concentration of 1 mg/mL, and 50 \( \mu \)g (50 \( \mu \)L) of the peptide was added to each of three placebo vials. Ethanol and Trolox® were added to the control and Trolox®, preparations as described in Example 11.

In addition, 100 \( \mu \)L phosphate buffered saline (PBS) was added to each preparation. The vials were reconstituted with 0.9-1.0 mL \( {^{99m}Tc} \) sodium pertechnetate (Techelite®) containing approximately 50 mCi \( {^{99m}Tc} \), and heated in a boiling water bath for ten hours.
minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 18.

**TABLE 18**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>0.5 hr</th>
<th>3 hr</th>
<th>6 hr</th>
<th>9 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>94.1</td>
<td>92.4</td>
<td>85.9</td>
<td>80.0</td>
</tr>
<tr>
<td>Trolox® (2 mg)</td>
<td>95.3</td>
<td>95.4</td>
<td>91.5</td>
<td>86.4</td>
</tr>
</tbody>
</table>

These results show that Trolox® increases the radiolabelling yield and the stability of a $^{99m}$Tc-labeled peptide chelator.

**EXAMPLE 13**

**Stabilization of a $^{99m}$Tc Bisamide Bisthiol Chelator by Trolox®**

Trolox® was tested for its ability to stabilize a $^{99m}$Tc-labelled non-peptide chelator (4-(butanoic acid)-2,2,9,9 tetramethyl-4,7-diaza-1,10-decanedithiol) having the structure.

![Chemical structure](image)

The non-peptide chelator was radiolabelled with $^{99m}$Tc in the presence and absence of Trolox® using the placebo vial heated preparation procedure as described in Example 11. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 19.

**TABLE 19**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>0.5 hr</th>
<th>3 hr</th>
<th>6 hr</th>
<th>9 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>48.5</td>
<td>56.5</td>
<td>54.0</td>
<td>52.9</td>
</tr>
<tr>
<td>Trolox® (2 mg)</td>
<td>88.6</td>
<td>79.1</td>
<td>78.3</td>
<td>77.0</td>
</tr>
</tbody>
</table>
These results show that Trolox® increases the radiolabelling yield and the stability of a $^{99m}$Tc-labelled non-peptide chelator.

**EXAMPLE 14**

**Stabilization of $^{99m}$Tc-labelled Depreotide by L-Methionine and Trolox®**

Lyophilized kit vials were prepared containing depreotide, L-methionine (Met), Trolox®, and other components as described in Table 20. All formulations were adjusted to pH 7.4 prior to lyophilization.

**TABLE 20**

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Trolox + Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depreotide</td>
<td>50 μg</td>
<td>50 μg</td>
</tr>
<tr>
<td>Sodium Glucoheptonate</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Dihydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edetate Disodium Dihydrate</td>
<td>100 μg</td>
<td>100 μg</td>
</tr>
<tr>
<td>Stannous Chloride</td>
<td>50 μg</td>
<td>50 μg</td>
</tr>
<tr>
<td>Dihydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trolox</td>
<td>-</td>
<td>2 mg</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>-</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

The lyophilized kits were radiolabelled with $^{99m}$Tc by reconstitution with 1.0 mL technetium $^{99m}$Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi $^{99m}$Tc and incubation at room temperature for 30 minutes following reconstitution. Some of the formulations were also radiolabelled in a heated preparation (heat in a boiling water bath for 10 minutes). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 21.
### TABLE 21

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Prep Type</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Heated</td>
<td>91.9</td>
<td>85.0</td>
<td>80.7</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>94.8</td>
<td>87.6</td>
<td>78.2</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>90.7</td>
<td>88.7</td>
<td>83.4</td>
</tr>
<tr>
<td></td>
<td>(Average)</td>
<td>(92.8)</td>
<td>(88.2)</td>
<td>(80.8)</td>
</tr>
<tr>
<td>Trolox (2 mg) + Met (5 mg)</td>
<td>Heated</td>
<td>92.0</td>
<td>93.4</td>
<td>94.1</td>
</tr>
<tr>
<td></td>
<td>Heated</td>
<td>92.9</td>
<td>93.3</td>
<td>93.2</td>
</tr>
<tr>
<td></td>
<td>Heated</td>
<td>93.6</td>
<td>90.7</td>
<td>91.5</td>
</tr>
<tr>
<td></td>
<td>(Average ± 1SD)</td>
<td>(92.8 ± 0.8)</td>
<td>(92.5 ± 1.5)</td>
<td>(92.9 ± 1.3)</td>
</tr>
<tr>
<td></td>
<td>Rm Temp</td>
<td>85.1</td>
<td>78.6</td>
<td>83.2</td>
</tr>
</tbody>
</table>

These results indicate that the combination of L-methionine and Trolox® increases the radiolabelling yield and the stability of $^{99m}$Tc depreotide prepared from formulated kits.

### EXAMPLE 15

**Stabilization of $^{99m}$Tc Depreotide by L-Methionine and Trolox® in Lyophilized Kit Preparations; Accelerated Temperature (40°C) Storage**

Lyophilized kits were prepared containing depreotide, L-methionine (Met) Trolox®, and other components as described in Table 20. All formulations were adjusted to pH 7.4 prior to lyophilization. The kits were stored for one week at 40°C. Some kits were also stored at -10°C as controls. The lyophilized kits were radiolabelled with $^{99m}$Tc in heated preparations as set forth above. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 22.
<table>
<thead>
<tr>
<th>Formulation</th>
<th>Storage Temp</th>
<th>Prep Type</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-10°C</td>
<td>Heated</td>
<td>-</td>
<td>82.6</td>
<td>77.8</td>
</tr>
<tr>
<td></td>
<td>40°C</td>
<td>Heated</td>
<td>-</td>
<td>82.6</td>
<td>79.0</td>
</tr>
<tr>
<td>Trolox + Met</td>
<td>40°C</td>
<td>Heated</td>
<td>86.1</td>
<td>86.5</td>
<td>87.0</td>
</tr>
</tbody>
</table>

These results indicate that the combination of L-methionine and Trolox® stabilizes $^{99m}$Tc-depreotide prepared from lyophilized kits which have been thermally stressed under conditions of accelerated temperature storage.

**EXAMPLE 16**

Stabilization of a $^{99m}$Tc Benzodiazepinedione Derivative by L-Methionine and Trolox in Lyophilized Kit Preparations

L-methionine and Trolox® were tested for their ability to stabilize a glycoprotein IIb/IIIa receptor-binding benzodiazepinedione derivative 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-amidinophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate, having the structure.

Lyophilized kit vials were prepared containing the benzodiazepinedione derivative and components as described in Table 23. All formulations were adjusted to pH 7.4 prior to lyophilization.
TABLE 23

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Trolox + Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivative</td>
<td>40 µg</td>
<td>40 µg</td>
</tr>
<tr>
<td>Sodium Glucoheptonate Dihydrate</td>
<td>25 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Edetate Disodium Dihydrate</td>
<td>100 µg</td>
<td>100 µg</td>
</tr>
<tr>
<td>Stannous Chloride Dihydrate</td>
<td>50 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>Trolox</td>
<td>-</td>
<td>2 mg</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>-</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

The lyophilized kits were radiolabelled with $^{99m}$Tc by reconstitution with 1.0 mL technetium $^{99m}$Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi $^{99m}$Tc and heating in a boiling water bath for 10 minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 24.

TABLE 24

<table>
<thead>
<tr>
<th>Formulation</th>
<th>0.5 hr</th>
<th>3.5 hr</th>
<th>6.5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>93.2</td>
<td>90.1</td>
<td>88.0</td>
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<td>93.6</td>
<td>94.5</td>
<td>88.8</td>
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<td>85.0</td>
<td>86.1</td>
<td>82.3</td>
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<tr>
<td>(Average ± 1SD):</td>
<td>(91.0 ± 4.1)</td>
<td>(90.0 ± 3.5)</td>
<td>(86.8 ± 3.0)</td>
</tr>
<tr>
<td>Trolox (2 mg) + Met (5 mg)</td>
<td>92.5</td>
<td>92.9</td>
<td>90.3</td>
</tr>
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<td>93.9</td>
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<tr>
<td></td>
<td>94.1</td>
<td>93.6</td>
<td>90.9</td>
</tr>
<tr>
<td>(Average ± 1SD):</td>
<td>(93.5 ± 0.9)</td>
<td>(93.5 ± 0.5)</td>
<td>(91.4 ± 1.4)</td>
</tr>
</tbody>
</table>

These results indicate that the combination of L-methionine and Trolox® increases the radiolabelling yield and the stability of the $^{99m}$Tc-labelled benzodiazepinedione derivative prepared from formulated kits.

It should be understood that the foregoing disclosure emphasizes certain specific embodiments of the invention and that all modifications or equivalents thereto are within the spirit and scope of the invention as set forth in the appended claims.
CLAIMS

1. A composition comprising a radiopharmaceutical precursor and a stabilizing amount of a stabilizer selected from the group consisting of:

   (a) a hydrophilic thioether;
   (b) a hydrophilic 6-hydroxy-chroman derivative; and
   (c) a mixture of said thioether and said 6-hydroxy-chroman derivative.

2. The composition of claim 1, wherein the thioether is selected from the group consisting of D-methionine, L-methionine, 3-(methylthio)propionaldehyde, D-ethionine, L-ethionine, 3-methylthio-1,2-propanediol, methyl-3-(methylthio)propionate, 2-(ethylthio)ethylamine, 2-(methylthio)- ethanol, buthionine, S-methyl-L-cysteine, S-methyl-D-cysteine, D-methioninol, and L-methioninol.

3. The composition of claim 2, wherein the thioether is selected from the group consisting of D-methionine, L-methionine, 2-(ethylthio)ethylamine, D-methioninol, L-methioninol, and 3-methylthio-1,2-propanediol.

4. The composition of claim 3, wherein the thioether is L-methionine.

5. The composition of any of claims 1 through 4, wherein the hydrophilic 6-hydroxy-chroman is selected from the group consisting of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid-4-sulfonic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-3-hydroxy-2-carboxylic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-glucosamine; and 6-hydroxy-2,5,7,8-tetramethylchroman-2-(carboxy- seryl-seryl-serylamide).

6. The composition of claim 5, wherein the hydrophilic 6-hydroxy-chroman is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.
7. The composition of any of claims 1 through 6, wherein the precursor comprises a targeting moiety selected from the group consisting of an antibody, a Fab antibody fragment, a F(ab')\textsubscript{2} antibody fragment, an epitope binding complementarity determining region derived from an antibody, a peptide, a growth factor, a receptor binding fragment of a growth factor, a hormone, a steroid, a receptor binding nucleic acid, a receptor binding monosaccharide, a receptor binding disaccharide, a receptor binding oligosaccharide, a receptor-binding lipid, a receptor binding benzodiazepine derivative, and a receptor binding antibiotic.

8. The composition of claim 7, wherein the targeting moiety is a peptide.

9. The composition of claim 7, wherein the targeting moiety is a glycoprotein IIb/IIIa receptor-binding benzodiazepine derivative.

10. The composition of claim 7, wherein the targeting moiety is a receptor binding benzodiazepine derivative.

11. The composition of any of claims 1 through 6, wherein the precursor comprises a peptide chelator.

12. The composition of any of claims 1 through 6, wherein the precursor comprises a non-peptide chelator.

13. The composition of any of claims 1 through 12, further comprising a radionuclide.

14. The composition of claim 13, wherein the radionuclide is selected from the group consisting of $^{125}$I, $^{131}$I, $^{211}$At, $^{47}$Sc, $^{67}$Cu, $^{72}$Ga, $^{90}$Y, $^{153}$Sm, $^{159}$Gd, $^{165}$Dy, $^{166}$Ho, $^{175}$Yb, $^{177}$Lu, $^{212}$Bi, $^{213}$Bi, $^{68}$Ga, $^{99m}$Tc, $^{111}$In, and $^{125}$I.
15. A composition according to any of claims 1 through 8, wherein the targeting moiety is a peptide selected from the group consisting of:

GGCSIPPEVKFNKPFVYLamide (SEQ ID NO:1);
GGCSIPPEVKFNKPFVYLI (SEQ ID NO:2);
GGCGFL (SEQ ID NO:3);
RGCSIPPEVKFNKPFVYLamide (SEQ ID NO:4);
RGCGHRPLDKKKREEAPSLRPAPPISGGYRamide (SEQ ID NO:5);
GGCRKKPQQFFGLMamide (SEQ ID NO:6);
GGCFVYLamide (SEQ ID NO:7);

(acetyl.TKPRGG)2K(ε-K)GCamide;
FDPFYWDKTFT(ε-K)GCamide;
acetyl.FDPFYWDKTFT(ε-K)GCamide;
acetyl.NalD.Cpa.YWDKTFT(ε-K)GCKKamide;
acetyl.FDPFYWDKTFTGGG(ε-K)GCamide;

acetyl.KKKKK.NalD.Cpa.YWDKTFT(ε-K)GCamide;
acetyl.DDFD.Cpa.YWDKTFT(ε-K)GCKKamide;
acetyl.DDFD.Cpa.YWDKTFT(ε-K)GCKKamide;
acetyl.KKKKK.NalD.Cpa.YWDKTFT(ε-K)GCKKamide;

acetyl.NalD.Cpa.YWDKTFT(ε-K)GCKKamide;
acetyl-DDDD.NalD.Cpa.YWDKTFT(ε-K)GCKKamide;
acetyl.DDFD.Cpa.YWDKTFT(ε-K)GCKKamide;
(DTPA).FDPFYWDKTFT(ε-K)GCamide;
(DTPA).NalD.Cpa.YWDKTFT.NalT(ε-K)GCKKamide;

(DTPA).(ε-K)GCFDFYWDKTFTamide;
(DTPA).(ε-K)GCFD.Cpa.YWDKTFTamide;
(DTPA).FDP.Cpa.YWDKTFT(ε-K)GCamide;
(DTPA).NalD.Cpa.YWDKTFT(ε-K)Gamide;
(DTPA).Aca.FD.Cpa.YWDKTFT(ε-K)Gamide;

(DTPA).NalD.Cpa.YWDKTFT.NalT(ε-K)GCKKamide;
(DTPA).NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
CH3.CO.FFWpKTFC(ε-K)GC.amide;
CH3.CO.FFWpKTFCCKKKK(ε-K)GC.amide;
CH3.CO.FFWpKTFC(ε-K)KKKKKGC.amide;

5 AKCGGGFpFYWpKTFT.amide;
AKCGGGFpYWpKTFT.amide;
DDDD.NalD.Cpa.YWpKTFT(ε-K)GCKKKK.amide;
DDD.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;

10 Trc.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
Hca.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
(Trc)2.NalD.Cpa.YWpKTFT(ε-K)GCKK.amide;
KKKK.NalD.Cpa.YWpKTFT(ε-K)GCDDDD.amide;
Kp.NalD.Cpa.YWpKTFT(ε-K)GCD.amide;

15 KpK.NalD.Cpa.YWpKTFT(ε-K)GCD.amide;
KpKK.NalD.Cpa.YWpKTFT(ε-K)GCD.amide;
KpKK.NalD.Cpa.YWpKTFT(ε-K)GCD.amide;
KpKKK.NalD.Cpa.YWpKTFT(ε-K)GCD.amide;
KpKKK.NalD.Cpa.YWpKTFT(ε-K)GCKDKD.amide;

20 KpKFKpD.Cpa.YWpKTF.Nal.(ε-K)GCDDDD.amide;
K(BAT).NalD.CMeYWpKVCMeT.amide
KpDKD.NalD.Cpa.YWpKTFT(ε-K)GCKDKD.amide;
KDKD.NalD.Cpa.YWpKTFT(ε-K)GCKDKD.amide;
Fp.Cpa.YWpKTC(ε-K)GCKK.amide;

25 Fp.Cpa.YWpKTC(ε-K)GC.amide;
Fp.Cpa.YWpKTFT(ε-K)GCKK.amide;
Fp.Cpa.YWpKTFTGGG(ε-K)GC.amide;
Fp.Cpa.YWpKTFT(ε-K)GCR.amide;
(Trc-imide), NalD, Cpa, YW₂KTFT(ε-K)GCR.amide;
Trc.(Trc-imide), K, NalD, Cpa, YW₂KTFT(ε-K)GCR.amide;
(Trc-imide)_2K, NalD, Cpa, YW₂KTFT(ε-K)GCR.amide;
(Trc-imide)_2K, NalD, Cpa, YW₂KTFT(ε-K)GCR.amide;

5 D₂DFD, Cpa, YW₂KTFT(ε-K)GCKK.amide;
D₂F, Cpa, YW₂KTFT(ε-K)GCKK.amide;
F₂FYW₂KTFT(ε-K)GCKK.amide;
AKCGGGF₂YW₂KTFT.amide;
(2-ketogulonyl), NalD, Cpa, YW₂KTFT(ε-K)GCKKamide;

10 (2-ketogulonyl), F₂, Cpa, YW₂KTFT(ε-K)GC.amide;
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.GC.Dap.Dap.amide);
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.(γ-Dab)KCR.amide);
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.KKKK(ε-K))GC.amide;
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.(ε-K)GCK.amide;

cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.(β-Dap)KCR.amide);
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.(β-Dap)KCK.amide;
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.(δ-Omm)GCK.amide;
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.(β-Dap)GCK.amide;
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.K(ε-K)KCK.amide;

cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.(ε-K)GCKK.amide;
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.K(ε-K)GCKK.amide;
cyclo-(N-(CH₃)₂FYW₂KV.Hcy(CH₃CO.K(ε-K)GC.amide;
RGCQAPLYKKI/KKLLES (SEQ ID NO:8);
acetyl.KK(ε-K)GCG CGG PLYKKI/KKLLES;

25 acetyl.KKKKK(ε-K)GCG GPLYKKI/KKLLES;
(CH₃CO.YD.Amp.GDC.KGCG.amide)₂(CH₃CO)₂K(ε-K)GC.amide;
(CH₃CO.YD.Amp.GDC.GGC Amn.GC Amn.GGCG.amide)₂(CH₃CO)₂K(ε-K)GC.amide;
(CH₃CO.YD.Ape.GDC.KGCG.amide)₂(CH₃CO)₂K(ε-K)GC.amide;
{(CH₃CO.YD.Ape.GDC.GGC GCG.amide)(CH₃CO)}₂K(ε-K)GC.amide;
(CH₃CO)₂Y₄D.Ac,-GDCGGCG, K(ε-K)GC, β-Alaamide;
(CH₃CO)₂Y₄D.Ac,-GDCGGCG, K(ε-K)GC, β-Alaamide;
{(CH₃CO)₂Y₄D.Ac,-GDCGGCG, K2(ε-K)GC,amide;
{(CH₃CO)₂Y₄D.Ac,-GDCGGCG, K2(ε-K)GC,amide;
{(CH₃CO)₂Y₄D.Ac,-GDCGGCG, K2(ε-K)GC,amide;
HSDAVFTDNYTRKQMAVKKYLNSILGC(ε-K)GC,amide;
HSDAVFTDNYTRKQMAVKKYLNSILNGGC.amide (SEQ ID NO:9);
AGCHSDAVFTDNYTRKQMAVKKYLNSILGC.amide (SEQ ID NO:10);
HSDAVFTDNYTRKQMAVKKYLNSILNC(BAT).amide (SEQ ID NO:11);
CH₃CO.SNLST.HheVGLKSC(BAT)ELHKLQYPRTNTGSFTP.amide (SEQ ID NO:12);
CH₃CO.SNLST.HheVGLKSC(BAT)ELHKLQYPRTNTGSFTP.amide (SEQ ID NO:12);
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
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CH₃CO.SNLST.HheVGLKSLQELHKLQYPRTNTGSFTP.amide (ε-K)GC,amide;
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SNLST.AsuVGLKSLQELHKLQYPRTNTGSFTP.amide;
SNLST.AsuVGLKSLQELHKLQYPRTNTGSFTP.amide;
SNLST.AsuVGLKSLQELHKLQYPRTNTGSFTP.amide;
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-Ch₃)Hcy(CH₃CO-β-Dap-Tyr-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-Ch₃)Hcy(CH₃CO-β-Dap-Phe(4-F)-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-Ch₃)Hcy(CH₃CO-β-Dap-Phe(4-NH₂)-Cys-Thr-Ser);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-Ch₃)Hcy(CH₃CO-β-Dap-Dap-Cys-Thr);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-Ch₃)Hcy(CH₃CO-β-Dap-Dap-Phe(4-NH₂)-Cys-Thr);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-Ch₃)Hcy(CH₃CO-β-Dap-Dap-Phe(4-NH₂)-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-Ch₃)Hcy(CH₃CO-β-Dap-His-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Arg-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Gly-Cys-Lys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Ser-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Dab-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Gly-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Dab-Cys-Ser(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-Lys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-Arg-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Lys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Arg-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Lys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-Dap-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-NH(CH₂CH₂O)₂CH₂CH₂NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Ser-Cys-Thr-NH(CH₂CH₂O)₂CH₂CH₂NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Lys-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Lys-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Lys-Gly-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Dab-Cys-Ser(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Dap-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-His-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Gly-Gly-Cys-Phe(4-NH₂)-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Om-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Dap-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Lys-Cys-Thr(ol));
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Ser-Ser-Cys-NHCH₂CH₂OCH₂CH₂NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Lys-Cys-NH₂);
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-β-Dap-Lys-Gly-Cys-NH₂); and
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH₃)Hcy(CH₂CO-Thr-Gly-Gly-Cys-NH₂).
16. The composition of claim 15, wherein the stabilizer consists only of a thioether and said thioether is methionine.

17. The composition of claim 16, wherein the peptide is \( \textit{cyclo-(N-CH}_3\textit{FYW}_D\textit{KV.Hcy(CH}_3\textit{CO.}(\beta-Dap)KCK.amide).} \)

18. The composition of claim 16, wherein the peptide is \( \textit{cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH}_3\textit{)Hcy(CH}_3\textit{CO-}\beta\textit{-Dap-Phe(4-NHz)-Cys-Thr-Ser).} \)

19. The composition of claim 15, wherein the stabilizer consists only of a 6-hydroxy-chroman derivative and said 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

20. The composition of claim 19, wherein the peptide is \( \textit{cyclo-(N-CH}_3\textit{FYW}_D\textit{KV.Hcy(CH}_3\textit{CO.}(\beta-Dap)KCK.amide).} \)

21. The composition of claim 15, wherein the stabilizer is a mixture of methionine and 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

22. The composition of claim 21 wherein the peptide is \( \textit{cyclo-(N-CH}_3\textit{FYW}_D\textit{KV.Hcy(CH}_3\textit{CO.}(\beta-Dap)KCK.amide).} \)

23. The composition of any of claims 15 through 22, further comprising a radionuclide.

24. The composition of claim 23, wherein the radionuclide is \( ^{99m}\text{Te.} \) \( \textit{cyclo-(N-CH}_3\textit{FYW}_D\textit{KV.Hcy(CH}_3\textit{CO.}(\beta-Dap)KCK.amide).} \)
25. A composition comprising a hydrophilic thioether and a benzodiazepine derivative having a structure:

![Chemical Structure](image)

5

26. The composition of claim 25, wherein the thioether is methionine.

27. A composition comprising a hydrophilic 6-hydroxy-chroman derivative and 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-amidinophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate.

10

28. The composition of claim 27, wherein the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

29. A composition comprising a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, and a benzodiazepine derivative having a structure:

![Chemical Structure](image)
30. The composition of claim 29, wherein the thioether is methionine and the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

31. The composition of any of claims 25 through 30, further comprising $^{99mTc}$. 

32. A method of stabilizing a radiopharmaceutical comprising the steps of:
   a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic thioether in a container; and
   b) adding a radionuclide to the container.

33. The method of claim 32, wherein the thioether is methionine.

34. A method of stabilizing a radiopharmaceutical comprising the steps of:
   a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative in a container; and
   b) adding a radionuclide to the container.

35. The method of claim 34, wherein the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

36. A method of stabilizing a radiopharmaceutical comprising the steps of:
   a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative in a container; and
   b) adding a radionuclide to the container.

37. The method of claim 36, wherein the thioether is methionine and the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.
38. The method of any of claims 32 through 37, wherein the radionuclide is $^{99m}$Tc.

39. A kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic thioether.

40. The kit of claim 39, wherein the thioether is methionine.

41. The kit of claim 40, wherein the precursor is cyclo-(N-CH$_3$)FYW$_2$KV.Hcy(CH$_2$CO.(β-Dap)KCKamide).

42. The kit of claim 40, wherein the precursor is cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH$_3$)Hcy(CH$_2$CO-β-Dap-Phe(4-NH$_2$)-Cys-Thr-Ser).

43. The kit of claim 40, wherein the precursor is

![Chemical Structure](image)

44. A kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative.

45. The kit of claim 44, wherein the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.
46. The kit of claim 45, wherein the precursor is 
\textit{cyclo-(N-CH₃)FYW₃KV.Hcy(CH₃CO.(β-Dap)KCK.amide).}

47. The kit of claim 45, wherein the precursor is: 
\[1-(\text{carboxyglycyl-glycyl-glycyl-cysteinamide})\text{methyl}]\-4-(2\text{-carboxyethyl})\-7\-[(4\text{-amidinophenyl})\text{methyl}]\-3,4\text{-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate.}\]

48. A kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative

49. The kit of claim 48, wherein the thioether is methionine and the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

50. The kit of claim 49, wherein the precursor is \textit{cyclo(N-CH₃)FYW₃KV.Hcy(CH₃CO.(β-Dap)KCK.amide).}

51. The kit of claim 49, wherein the precursor is
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**STABILIZATION OF RADIOPHARMACEUTICAL COMPOSITIONS USING HYDROPHILIC THIOETHERS AND HYDROPHILIC 6-HYDROXY CHROMANS**

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X is Hhc, homocysteine

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peptide is cyclized thru thioether

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