P/00/008
Section 29(1)
Regulation 3.1(2)

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

We, **MALLINCKRODT MEDICAL, INC.**, of 675 McDonnell Blvd, P.O. Box 5840, St Louis, MO 63134, United States of America, being the applicant in respect of Application No. 80947/91, state the following:-

The person nominated for the grant of the patent:

has entitlement from the actual inventor by assignment

The person nominated for the grant of the patent:

has entitlement from the applicant of the application listed in the declaration under Article 8 of the PCT by assignment

The basic application listed in the declaration made under Article 8 of the PCT:

is the first application made in a Convention country in respect of the invention

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Dated : 24 February 1995

CARTER SMITH & BEADLE
Patent Attorneys for the Applicant

TO: *The Commissioner of Patent*
Our Ref: *#12934 BMH:SM*

AU9180947

(12) PATENT ABRIDGMENT (11) Document No. AU-B-80947/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 658826

(54) Title
TECHNETIUM-99M COMPLEX FOR EXAMINING THE RENAL FUNCTION

International Patent Classification(s)
(51)[5] C07F 013/00 A61K 049/02 C07C 323/66 C07F 009/38

(21) Application No. : 80947/91 (22) Application Date : 03.05.91

(87) PCT Publication Number : WO92/07859

(30) Priority Data

(31) Number	(32) Date	(33) Country
605640	29.10.90	US UNITED STATES OF AMERICA

(43) Publication Date : 26.05.92

(44) Publication Date of Accepted Application : 04.05.95

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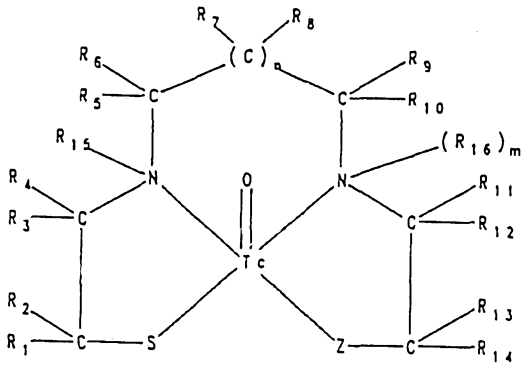
(56) Prior Art Documents
US 4444690
US 4849511
US 4925650

(57) Claim

1. A technetium-99m radiopharmaceutical complex for examining the renal function, said complex having the formula:



wherein

each of the symbols R_1-R_{16} is individually selected from the group consisting of hydrogen, straight or branched, unsubstituted or substituted alkyl having 1-4 carbon atoms, ACOOH, ASO_3H, and APO_3H_2, wherein A is a straight or branched, unsubstituted or substituted alkyl group having 0-4 carbon atoms and wherein H may be replaced with

.../2

suitable, pharmaceutically acceptable, positively charged ions such as Na^+, K^+, Li^+, Ca^{2+}, or Sr^{2+};

Z is a sulphur atom or an amino group of the general formula R_{17}-N-$(R_{18})_k$, wherein k is 0 or 1 and R_{17} and R_{18} have the same meanings as the symbols R_1-R_{16};

R_3 together with R_4, R_5 together with R_6, R_9 together with R_{10}, or R_{11} together with R_{12}, additionally may form an oxygen atom;

Tc represents technetium-99m;

n is 0 or 1; and

m is 0 or 1;

with the provisos that

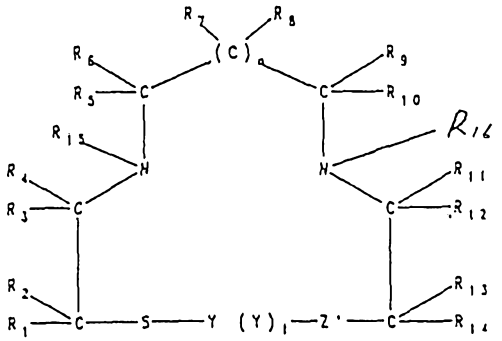
if any of the symbols R_{15}-R_{18} is ACOOH, ASO_3H, or APO_3H_2, then A is a straight or branched, unsubstituted or substituted alkyl group having 1-4 carbon atoms;

at least one of the symbols R_1-R_{18} is ACOOH; and

at least one of the symbols R_1-R_{18} is ASO_3H, or APO_3H_2.

10. A method of making a radiopharmaceutical complex from a kit, said method comprising:

providing a kit which includes a ligand having the formula:



wherein

each of the symbols R_1-R_{16} is individually selected from the group consisting of hydrogen, straight or branched, unsubstituted or substituted alkyl having 1-4 carbon atoms, ACOOH, ASO_3H, and APO_3H_2, wherein A is a straight or branched. unsubstituted or substituted alkyl group having 0-4 carbon

atoms and wherein H may be replaced with suitable, pharmaceutically acceptable, positively charged ions such as Na^+, K^+, Li^+, Ca^{2+}, or Sr^{2+};

Z' is either a sulphur atom or an amino group having the general formula R_{17}-N-R_{18}, wherein R_{17} and R_{18} have the same meanings as the symbols R_1-R_{16};

Y is a hydrogen atom or a suitable protecting group; and

R_3 together with R_4, R_5 together with R_6, R_9 together with R_{10} or R_{11} together with R_{12}, additionally may form an oxygen atom;

n is 0 or 1; and

l is 0 or 1;

with the provisos that

if Z' is a sulphur atom, then l = 1; and

if Z' is a amino group, then l = 0;

if any of the symbols R_{15}-R_{18} is ACOOH, ASO_3H or APO_3H, then A is a straight or branched unsubstituted or substituted alkyl group having 1 to 4 carbon atoms;

at least one of the symbols R_1 to R_{18} is ACOOH; and

at least one of the symbols R_1 to R_{18} is ASO_3H or APO_3H; and

combining said kit with a radionuclide solution;

wherein said ligand binds to said radionuclide to form said radiopharmaceutical complex.

OPI DATE 26/05/92 APPLN. ID 80947 / 91
AOJP DATE 09/07/92 PCT NUMBER PCT/US91/03076

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07F 13/00, A61K 49/02
C07F 9/38, C07C 323/66

A1

(11) International Publication Number: WO 92/07859

(43) International Publication Date: 14 May 1992 (14.05.92)

(21) International Application Number: PCT/US91/03076

(22) International Filing Date: 3 May 1991 (03.05.91)

(30) Priority data:
605,640 29 October 1990 (29.10.90) US

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: TECHNETIUM-99m COMPLEX FOR EXAMINING THE RENAL FUNCTION

(57) Abstract

The present invention relates to novel technetium-99m complexes and to methods of preparing the complexes. The present invention further relates to radiopharmaceutical compositions comprising the complexes, to the use of the compositions for examining the renal function, and to a kit for preparing such compositions.

TECHNETIUM-99m COMPLEX FOR EXAMINING THE RENAL FUNCTION

The present invention relates to a technetium-99m complex and to a method of preparing the complex. The present invention further relates to a radiopharmaceutical composition comprising the complex, to the use of the composition for examining the renal function, and to a kit for preparing such a composition.

Radioactive labelled compounds are used for the examination of patients, for example, into deviations in shape and function of internal organs and into the presence and location of pathological processes in the body. For this purpose, a composition in which the radioactive compound is present is administered to the patient, for example, in the form of an injectable liquid. By means of suitable detection apparatus, e.g. a gamma camera, images can be obtained of, for example, the organ or the pathological process in which the radioactive compound has been incorporated, by recording the emitted radiation. Compounds which are generally used for examining the renal function are radioactive Tc-99m MAG_3, iodo-Hippuran® and Tc99m-diethylene triamine pentaacetic acid (DTPA), which will be discussed hereinafter.

In addition to the passive glomerular filtration, an active tubular secretion also takes place in the kidneys. The functioning of the kidneys is determined to a considerable extent by this active filtration. In an adult person approximately 125 ml of blood plasma per minute is purified by glomerular filtration. This means that the clearance is 125 ml per minute. The total clearance which can be effected by the kidneys is 600 to 700 ml of plasma per minute. It appears that the above-mentioned chelate of DTPA clears from the kidneys at a rate of 100 ml of blood plasma per minute, and therefore the chelate is eliminated entirely or substantially entirely by glomerular filtration

and hence is not very suitable for examining the renal function.

There exists a great need for a suitable composition for examining the renal function which is permanently available, in particular for kidney transplantation patients, accident victims and patients after large vascular operations.

An example of a radioactive iodo-Hippuran® compound generally used for examining the renal function is iodo-131-Hippuran®, which is secreted actively tubularly and hence is very suitable for examining the renal function as regards organ specificity. Further, iodo-131-Hippuran® is excellently suitable for the above applications, because of its ready availability. However, like all iodo-131 compounds, iodo-131-Hippuran® constitutes a serious radiation burden for the patient. Therefore, iodo-131 compounds can be administered to the patient only in restricted doses, as a result of which the resulting information is insufficient to obtain statistically reliable images of the renal function by means of a gamma camera.

Another radioactive iodo-Hippuran® compound frequently used for examining the renal function is iodo-123-Hippuran® which is excellently suitable as regards organ specificity and restricted radiation burden. Iodo-123-containing compositions, however, have only a restricted availability due to the short half-life, i.e. 13.3 hours, and because the production of iodo-123 must necessarily be carried out in a cyclotron.

Technetium-99m complexes which show a tubular secretion which is comparable to that of iodo-Hippuran® are

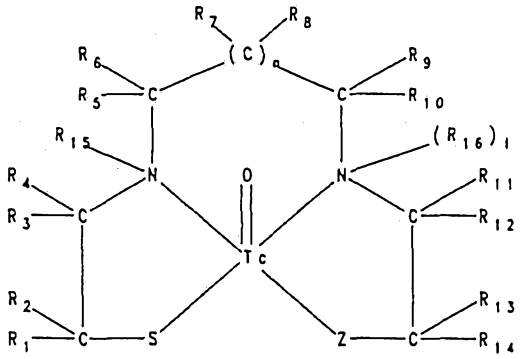
known from European Patent Application 173424. This application discloses the preparation of Tc-99m-mercaptoacetyltriglycine (Tc99m-MAG3), which complex is secreted by the kidneys selectively and approximately equally rapidly to Iodo-Hippuran®. However, the organ specificity of said complexes still leaves something to be desired. This is a disadvantage, especially when these compounds are used for function examination. Chemically related compounds having an improved organ specificity are the subject of the recently published European patent application 250013.

In connection with the comparatively short half-life of radionuclides it is often nearly impossible to deliver the ready-to-use labelled product to the user. In such cases it is desirable to place the various reaction components at the user's disposal in a so-called kit. By means of this kit, the user himself can carry out the labelling reaction with the radionuclide in the clinical hospital or laboratory at any desired moment. This is favorable in particular for preparing technetium-99m-labelled products, because most modern clinical hospitals or laboratories have at their disposal a molybdenum-technetium generator, from which the desired quantity of technetium-99m can very easily be obtained in the form of a pertechnetate solution. The process of preparing the technetium-99m-labelled product from the supplied kit must be able to be carried out by the user with a few simple manipulations, without laborious operations, and by using the facilities which are at his disposition in the clinic. Furthermore, the stability of the labelled product is of great importance. In fact, if the stability is not satisfactory, there is insufficient opportunity to be able to prepare and perform the renal function examination in patients carefully. Moreover, there is a constant risk

that if the shelf life is exceeded, a contaminated composition may be administered to the patient and the results of the examination will no longer be reliable.

It has now been found that the shelf life of technetium-99m complexes described in the European patent applications mentioned hereinbefore is at most a few hours, depending on the complex-forming ligands and the labelling method used. In practice this is often insufficient because it is desired to have a suitable composition available immediately at any instant of the day. Moreover, it is advantageous that a radioactive composition need be prepared only once daily. Furthermore the reaction conditions in which the user has to prepare the labelled product from the kit are not very favorable. In fact, in order to prepare the technetium-99m complexes described in the European patent applications, the kit constituents must be heated for at least 5 minutes with the eluate from a molybdenum-technetium generator on a boiling water bath to produce the desired reaction resulting in the formation of the technetium-99m complex. In carrying out this operation, the possibility of accidents in which radioactive material is released are very possible.

Technetium-99m complexes for examining the renal function have been previously described in United States Patent 4,925,650, which is hereby incorporated by reference. This patent describes technetium-99m complexes having the general formula:



(A)

wherein

- Z is a sulphur atom or an amino group of the general formula R_{17}-N-$(R_{18})_k$, in which k is 0 or 1 and R_{17} and R_{18} have the same meanings as the symbols R_1-R_{16};
- each of the symbols R_1-R_{16} is individually selected from the group consisting of hydrogen, straight or branched, unsubstituted or substituted alkyl having 1-4 carbon atoms, and ACOOH, wherein A is a straight or branched, unsubstituted or substituted alkyl group having 0-4 carbon atoms;
- and R_5 together with R_6 or R_9 together with R_{10} additionally may form an oxygen atom;
- Tc represents technetium-99m;
- t is 0 or 1; and
- n is 0 or 1;

with the provisos that

(a) if R_{15}, R_{16}, R_{17} and/or R_{18} are/is ACOOH, A is a straight or branched, unsubstituted or substituted alkyl group having 1-4 carbon atoms;

(b) at least one of the symbols R_1-R_{18} is ACOOH; and

(c) if t is 1, at least two of the symbols R_1-R_{18} is ACOOH;

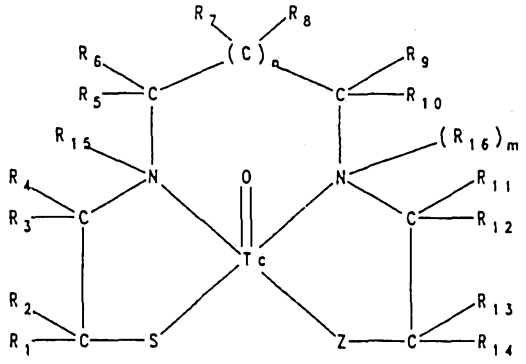
or a pharmaceutically acceptable salt of this compound.

It is one object of the present invention to provide a technetium-99m complex, suitable for examining the renal function, having a high organ specificity and an improved

stability, and which is suitable for preparation from a kit.

The objects of the present invention can be achieved, according to one embodiment of the present invention, by providing a technetium-99m complex which is similar to complexes defined by the general formula (A) above, but wherein certain substitutions have been made.

In particular, the present invention relates to technetium-99m complexes which satisfy the general formula:



(I)

wherein

- each of the symbols R_1-R_{16} is individually selected from the group consisting of hydrogen, straight or branched, unsubstituted or substituted alkyl having 1-4 carbon atoms, ACOOH, ASO_3H, and APO_3H_2, wherein A is a straight or branched, unsubstituted or substituted alkyl group having 0-4 carbon atoms and wherein H may be replaced with suitable, pharmaceutically acceptable, positively charged ions such as Na^+, K^+, Li^+, Ca^{2+}, or Sr^{2+};
- Z is a sulphur atom or an amino group of the general formula R_{17}-N-$(R_{18})_k$, in which k is 0 or 1 and R_{17} and R_{18} have the same meanings as the symbols R_1-R_{16};
- R_3 together with R_4, R_5 together with R_6, R_9 together

with R_{10}, or R_{11} together with R_{12}, additionally may form an oxygen atom;

- Tc represents technetium-99m;
- n is 0 or 1; and
- m is 0 or 1;

with the provisos that

(a) if any of the symbols R_{15}-R_{18} is ACOOH, ASO_3H, or APO_3H_2, then A is a straight or branched, unsubstituted or substituted alkyl group having 1-4 carbon atoms;

(b) at least one of the symbols R_1-R_{18} is ACOOH; and

(c) at least one of the symbols R_1-R_{18} is ASO_3H, or APO_3H_2.

When the above symbol k is 1, there is a coordinative bond between the amino-N and Tc. The coordinative bonds in the above formula (I) also occur when Z is a sulphur atom.

If the above symbols represent or include substituted alkyl groups, such substituents are preferably selected from hydroxy groups and acid groups or their salts; wherein examples of suitable acid groups are carboxy groups.

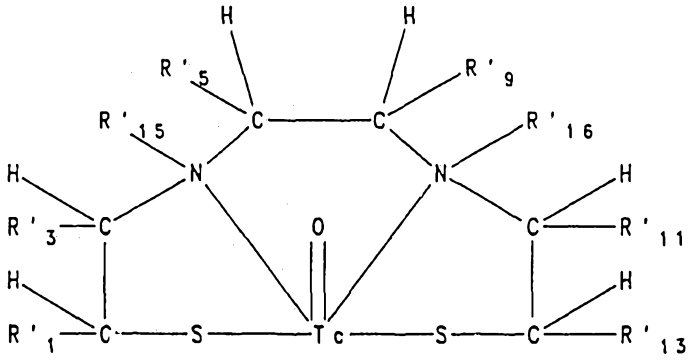
Pharmaceutically acceptable salts may be salts with ions of alkali metals, alkaline earths or suitable transition metals.

The new technetium-99m complexes will usually occur in stereoisomeric configurations which may differ in the biological properties. By starting from the stereochemically most suitable complex-forming ligands, stereoisomeric technetium complexes can be prepared having properties which are most favorable for the intended purpose.

While the technetium-99m complexes according to the present invention are similar to those previously described

in the United States Patent 4,925,650, it has now been discovered that certain substitutions may be made to those complexes which were not previously disclosed. In particular, the complexes according to the present invention include sulfonate or phosphonate groups at the R_1 to R_{16} sites.

A preferred technetium-99m complex according to the present invention, satisfies the general formula:



(II)

wherein

- each of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} is individually selected from the group consisting of hydrogen, methyl, $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, and $(CH_2)_qPO_3H_2$, wherein q is 0 or 1; and
- Tc represents technetium-99m;

with the provisos that

(a) if either of the symbols R'_{15}, or R'_{16} is $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$, then q is 1;

(b) at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}', R'_{13}, R'_{15}, or R'_{16} is $(CH_2)_qCOOH$;

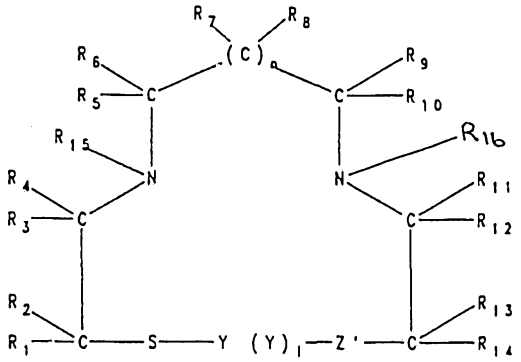
(c) at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}', R'_{13}, R_{15}' or R_{16}' is $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$; and

(d) at most four of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}', R'_{13}, R_{15}' or R_{16}' are $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$.

A technetium-99m complex according the invention is

generally used in the form of a composition which is suitable for examining the renal function. In addition to the radioactive complex, such a radiopharmaceutical composition will usually comprise a liquid, pharmaceutically acceptable carrier material, preferably a physiological saline solution. A radiodiagnostic examination can be performed with such a composition by administering the composition to a patient, in a quantity of 0.1 to 30 mCi, preferably of a 0.5 to 10 mCi, per 70 kg of body weight, and by then recording the radioactive radiation emitted by the living being by means of, for example, a gamma camera.

The invention further relates to a method of preparing a technetium-99m complex according to the invention by reacting technetium-99m in the form of a pertechnetate in the presence of a reducing agent and optionally a suitable chelator with a ligand of the general formula



(III)

wherein

- the symbols n and R_1-R_{16} have the same meanings given above in Formula (I);
- Z' is a sulphur atom or an amino group of the general formula R_{17}-N-R_{18}, wherein R_{17} and R_{18} have the same meanings given above in Formula (I);
- Y is a hydrogen atom or a suitable protecting group;

and

- l is 0 or 1;

with the provisos that,

(a) if Z′ is a sulphur atom, then l = 1; and

(b) if Z′ is a amino group, then l = 0.

Examples of suitable protective groups Y for the mercapto group are: acetyl, trifluoroacetyl, hydroxyacetyl, carboxyacetyl, acetamidomethyl, benzoyl, benzyl, benzoyl-aminomethyl and the like.

The reducing agent serves to reduce the Tc-99m pertechnetate which in a physiological saline solution is eluted from a molybdenum-technetium generator. Suitable reducing agents are, for example, dithionite, formamidine sulphinic acid, diaminoethane disulphinate or suitable metallic reducing agents such as Sn(II), Fe(II), Cu(I), Ti(III) or Sb(III); wherein Sn(II) has proved to be particularly suitable.

For the above-mentioned complex-forming reaction, technetium-99m is presented to the above-mentioned ligand as a salt or in the form of a chelate bound to comparatively weak chelators; in the latter case the desired technetium-99m complex is formed by ligand exchange. Examples of suitable chelators for the radionuclide are dicarboxylic acids, polycarboxylic acids or hydroxy carboxylic acids, such as oxalic acid, malonic acid, succinic acid, maleic acid, orthophthalic acid, malic acid, lactic acid, tartaric acid, citric acid, ascorbic acid, salicylic acid or derivatives of these acids; phosphorus compounds such as pyrophosphates; or enolates. Citric acid, tartaric acid, ascorbic acid, glucoheptonic acid or a derivative thereof are particularly suitable chelators for this purpose, because it appears that a

chelate of technetium-99m with of one these chelators particularly easily undergoes the desired ligand exchange.

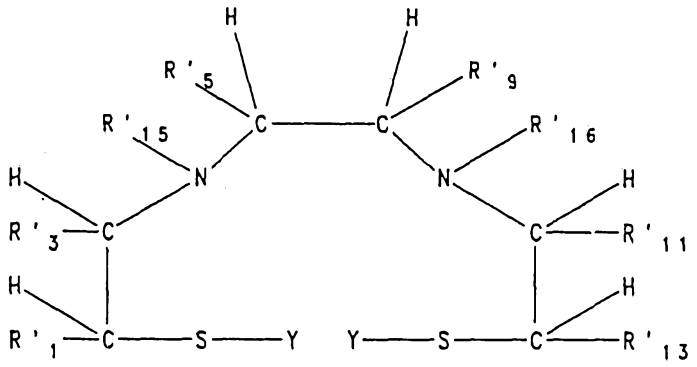
It has been found that the above-mentioned complex-forming reaction occurs quantitatively at room temperature i.e. with a radiochemical yield exceeding 98%. So heating of the reaction mixture is not necessary to reach a full conversion to the desired technetium-99m complex.

Since the radiopharmaceutical composition according to the invention can be prepared so easily and simply, the preparation can be carried out particularly readily by the user himself. The invention therefore also relates to a so-called kit, comprising (1) in an optionally dry condition a ligand of the above general formula III, wherein the symbols have the meanings given hereinbefore and to which optionally an inert, pharmaceutically acceptable carrier and/or auxiliary substances have/has been added, (2) a reducing agent and optionally a chelator, ingredients (1) and (2) being optionally combined, and (3) if desired, instructions for use with a prescription for carrying out the above-described method by reacting ingredients (1) and (2) with technetium-99m in the form of a pertechnetate solution.

Examples of suitable reducing agents and chelators for the above kit have been given hereinbefore. The pertechnetate solution can simply be obtained by the user himself from a molybdenum-technetium generator which is available to him. The above-mentioned ingredients (1) and (2) may be combined, provided they are compatible. Such a monocomponent kit, in which the combined ingredients are preferably lyophilized, is excellently suitable to be reacted by the user with the pertechnetate solution in a simple manner.

The constituent (1) of the above kits may be delivered as a solution, for example, in the form of a physiological saline solution, or in some buffer solution, but is preferably present in a dry condition, for example in a lyophilized condition. When used as a component for an injection liquid, it should be sterile, for example, if the constituent is present in a dry condition, the user should use a sterile physiological saline solution as a solvent. If desired, the above-mentioned constituent may be stabilized in a usual manner with suitable stabilizers such as ascorbic acid, gentisic acid or salts of these acids, or it may be provided with other auxiliary means such as fillers, e.g. glucose, lactose, mannitol, inositol, and the like.

The kit according to the invention preferably comprises a ligand of the general formula



(IV)

wherein

- the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} have the same meanings given above in Formula (II); and
- Y is a hydrogen atom or a suitable protecting group.

These complex-forming ligands can very easily be converted into the desired technetium-99m complexes.

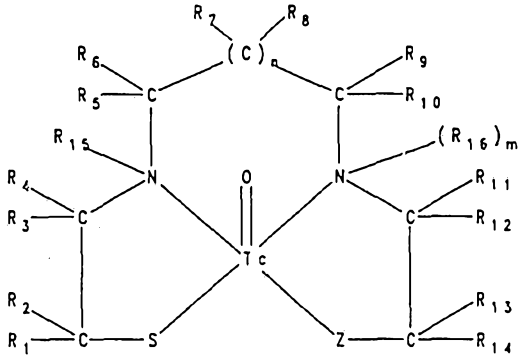
The stereochemical configuration of the technetium-99m

complex is determined by the configuration of the starting ligand of the above general formula III or IV. Different stereoisomers of these ligands can be separated from each other by using techniques known for this purpose such as recrystallization and/or chromatographic methods. If desired, for the separation the stereoisomer mixture may be converted with a stereochemically pure D- or L-isomer of a suitable amine, carboxylic acid, and the like, after which the isomer separation is carried out, succeeded by eliminating the used amine, carboxylic acid, etc. An alternative, also particularly suitable method of preparing stereochemically pure ligands, consists in using for the synthesis a starting material which is already stereochemically pure and which is easily available or obtainable as a stereoisomer, and in ensuring that during the synthesis of the intended ligand that the stereochemical purity is not lost, i.e. that no racmization occurs.

The foregoing has been a description of certain preferred embodiments of the present invention, but is not intended to limit the invention in any way. Rather, many modifications, variations and changes in details may be made within the scope of the present invention.

What is claimed is:

1. A technetium-99m radiopharmaceutical complex for examining the renal function, said complex having the formula:



wherein

each of the symbols R_1-R_{16} is individually selected from the group consisting of hydrogen, straight or branched, unsubstituted or substituted alkyl having 1-4 carbon atoms, ACOOH, ASO_3H, and APO_3H_2, wherein A is a straight or branched, unsubstituted or substituted alkyl group having 0-4 carbon atoms and wherein H may be replaced with suitable, pharmaceutically acceptable, positively charged ions such as Na^+, K^+, Li^+, Ca^{2+}, or Sr^{2+};

Z is a sulphur atom or an amino group of the general formula R_{17}-N-$(R_{18})_k$, wherein k is 0 or 1 and R_{17} and R_{18} have the same meanings as the symbols R_1-R_{16};

R_3 together with R_4, R_5 together with R_6, R_9 together with R_{10}, or R_{11} together with R_{12}, additionally may form an oxygen atom;

Tc represents technetium-99m;

n is 0 or 1; and

m is 0 or 1;

with the provisos that

if any of the symbols R_{15}-R_{18} is ACOOH, ASO_3H, or APO_3H_2, then A is a straight or branched, unsubstituted or substituted alkyl group having 1-4 carbon atoms;

at least one of the symbols R_1-R_{18} is ACOOH; and

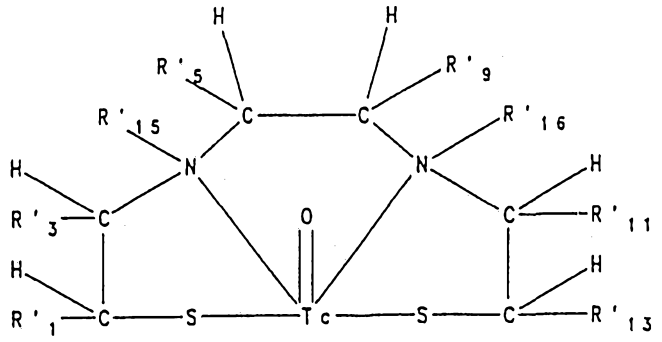
at least one of the symbols R_1-R_{18} is ASO_3H, or APO_3H_2.

2. A complex according to claim 1, wherein said substituted alkyl group is selected from the group consisting of hydroxy groups and acid groups, or their salts.

3. A complex according to claim 2, wherein said acid group is carboxy group.

4. A complex according to claim 2, wherein said salts may be pharmaceutically acceptable salts with ions of alkali metals, alkaline earths, or suitable transition metals.

5. A complex according to claim 1, having the formula:



wherein

each of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} is individually selected from the group consisting of hydrogen, methyl, $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, and $(CH_2)_qPO_3H_2$, wherein q is 0 or 1; and

Tc represents technetium-99m;

with the provisos that

if either of the symbols R'_{15}, or R'_{16} is $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$, then q is 1;

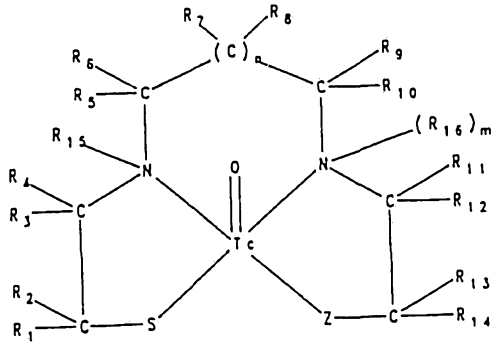
at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} is $(CH_2)_qCOOH$;

at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} is $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$; and

at most four of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} are $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$.

6. A method of examining the renal function using a radiopharmaceutical complex comprising:

providing a radiopharmaceutical complex having the formula:



wherein

each of the symbols R_1-R_{16} is individually selected from the group consisting of hydrogen, straight or branched, unsubstituted or substituted alkyl having 1-4 carbon atoms, ACOOH, ASO_3H, and APO_3H_2, wherein A is a straight or branched, unsubstituted or substituted alkyl group having 0-4 carbon atoms and wherein H may be replaced with suitable, pharmaceutically acceptable, positively charged ions such as Na^+, K^+, Li^+, Ca^{2+}, or Sr^{2+};

Z is a sulphur atom or an amino group of the general formula R_{17}-N-$(R_{18})_k$, wherein k is 0 or 1 and R_{17} and R_{18} have the same meanings as the symbols R_1-R_{16};

R_5 together with R_6 or R_9 together with R_{10} additionally may form an oxygen atom;

Tc represents technetium-99m;

n is 0 or 1; and

m is 0 or 1;

with the provisos that

if any of the symbols R_{15}-R_{18} is ACOOH, ASO_3H, or APO_3H_2, then A is a straight or branched, unsubstituted or substituted alkyl group having 1-4 carbon atoms;

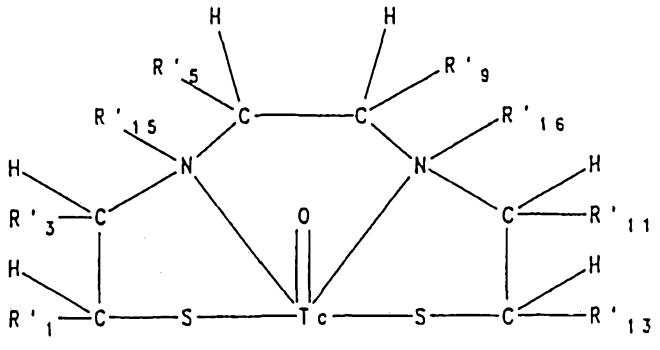
at least one of the symbols R_1-R_{18} is ACOOH; and

at least one of the symbols R_1-R_{18} is ASO_3H, or APO_3H_2;

administering an effective amount of said radiopharmaceutical complex to a living being; and

scanning said living being with detection means to detect said administered radiopharmaceutical complex.

7. A method according to claim 6, wherein said complex has the formula:



wherein

Each of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} is individually selected from the group consisting of hydrogen, methyl, $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, and $(CH_2)_qPO_3H_2$, wherein q is 0 or 1; and

Tc represents technetium-99m;

with the provisos that

if either of the symbols R'_{15}, or R'_{16} is $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$, then q is 1;

at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, or R'_{16} is $(CH_2)_qCOOH$;

at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, or R'_{16} is $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$; and

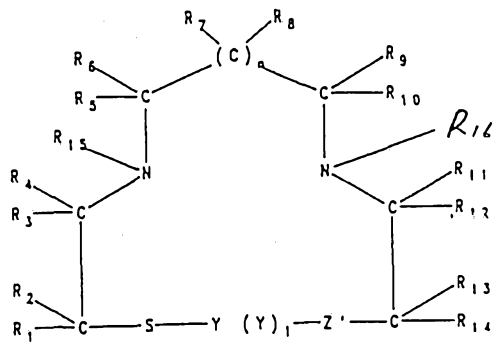
at most four of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, or R'_{16} are $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, or $(CH_2)_qPO_3H_2$.

8. A method according to claim 6, wherein said complex is administered in a quantity of 0.5 to 30 mCi per 70 kg of body weight.

9. A method according to claim 8, wherein said complex is administered in a quantity of 0.5 to 10 mCi per 70 kg of body weight.

10. A method of making a radiopharmaceutical complex from a kit, said method comprising:

providing a kit which includes a ligand having the formula:



wherein

each of the symbols R_1-R_{16} is individually selected from the group consisting of hydrogen, straight or branched, unsubstituted or substituted alkyl having 1-4 carbon atoms, ACOOH, ASO_3H, and APO_3H_2, wherein A is a straight or branched, unsubstituted or substituted alkyl group having 0-4 carbon atoms and wherein H may be replaced with suitable, pharmaceutically acceptable, positively charged ions such as Na^+, K^+, Li^+, Ca^{2+}, or Sr^{2+};

Z' is either a sulphur atom or an amino group having the general formula R_{17}-N-R_{18}, wherein R_{17} and R_{18} have the same meanings as the symbols R_1-R_{16};

Y is a hydrogen atom or a suitable protecting group; and

R_3 together with R_4, R_5 together with R_6, R_9 together with R_{10} or R_{11} together with R_{12}, additionally may form an oxygen atom;

n is 0 or 1; and

l is 0 or 1;

with the provisos that

if Z' is a sulphur atom, then l = 1; and

if Z' is a amino group, then l = 0;

if any of the symbols R_{15}-R_{18} is ACOOH, ASO_3H or APO_3H, then A is a straight or branched unsubstituted or substituted alkyl group having 1 to 4 carbon atoms;

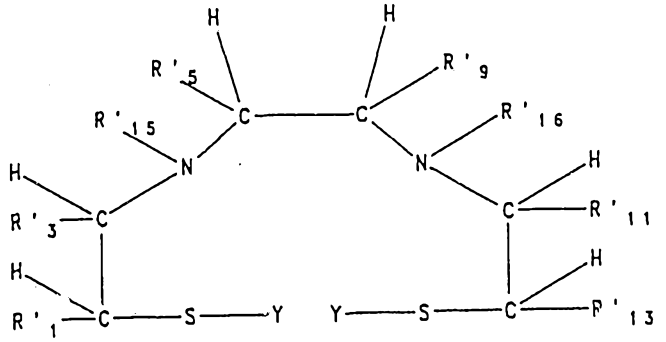
at least one of the symbols R_1 to R_{18} is ACOOH; and

at least one of the symbols R_1 to R_{18} is ASO_3H or APO_3H; and

combining said kit with a radionuclide solution;

wherein said ligand binds to said radionuclide to form said radiopharmaceutical complex.

11. A method according to claim 10, wherein said ligand has the formula:



wherein

each of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15}, and R'_{16} is individually selected from the group consisting of hydrogen, methyl, $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$, and $(CH_2)_qPO_3H_2$, wherein q is 0 or 1; and

Y is hydrogen or a suitable protecting group;

with the provisos that if either of the symbols R'_{15} or R'_{16} is $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$ or $(CH_2)_qPO_3H_2$, then q is 1;

at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15} or R'_{16} is $(CH_2)_qCOOH$;

at least one of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15} or R'_{16} is $(CH_2)_qSO_3H$ or $(CH_2)_qPO_3H_2$; and

at most four of the symbols R'_1, R'_3, R'_5, R'_9, R'_{11}, R'_{13}, R'_{15} or R'_{16} are $(CH_2)_qCOOH$, $(CH_2)_qSO_3H$ or $(CH_2)_qPO_3H_2$.

12. A method according to claim 10, wherein said radionuclide solution is a pertechnetate solution.

13. A technetium-99m radiopharmaceutical complex according to any one of claims 1 to 5 substantially as hereinbefore described.

DATED: 16 February 1995

CARTER SMITH & BEADLE
Patent Attorneys for the Applicant:
MALLINCKRODT MEDICAL, INC.

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 F 13/00 A 61 K 49/02 C 07 F 9/38
C 07 C 323/66

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 F 13/00 A 61 K 49/00 C 07 F 9/00 C 07 C 323/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US,A,4925650 (D.L. NOSCO et al.) 15 May 1990, see the whole document (cited in the application)	6-8
Y		1-5,9-28
X	EP,A,0250013 (MALLINCKRODT, INC.) 23 December 1987, see the whole document (cited in the application)	6-8
Y		1-5,9-28
A	US,A,4444690 (A.R. FRITZBERG) 24 April 1984, see the whole document	1-28

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11-09-1991	07. 10. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 29 - 32 because they relate to subject matter not required to be searched by this Authority, namely:

Please see RULE 39.1 (iv) - PCT:
.. methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a)

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9103076 SA 48363

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/10/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4925650	15-05-90	CA-A- 2002850	16-05-90
EP-A- 0250013	23-12-87	AU-B- 611854	27-06-91
		JP-A- 62289596	16-12-87
		US-A- 4849511	18-07-89
US-A- 4444690	24-04-84	None	