

Description

Technical Field

The present invention relates to cationic lipophilic complexes having utility as brain, myocardial, pancreas and hepatobiliary imaging agents.

Background Art

In recent years diagnostic nuclear medicine has proven to be of enormous value to the medical community. Procedures for imaging, and therefore detecting abnormalities in the brain, liver, lungs, bones, and the like, have been well developed and are routinely used. These procedures are based on the tendency of the body to concentrate some chemical form of a particular gamma ray emitting isotope in the organ of interest; subsequent scanning of the organ with a gamma ray camera provides an image of the organ from which diagnostic information can be obtained. It is clear that the radioisotope with optimum nuclear properties (half-life, gamma ray energy, and the like) for medical gamma ray scanning is ^{99m}Tc . It is therefore desirable to develop various chemical forms of Tc that will (a) concentrate in organs for which no satisfactory imaging agent has yet been found and/or (b) show greater organ specificity than the imaging agents currently available.

The metastable isotope Tc-99m has a 6 hour half-life and an emission spectrum, 99% gamma radiation of 140 KeV, which is well suited for techniques of diagnostic nuclear medicine. Tc-99m has a high specific activity, 5.28×10^8 millicuries per gram and a convenient rapid rate of decay; whereas its daughter product, Tc-99, has a specific activity which is almost 9 orders of magnitude lower and a half-life which is roughly 8 orders of magnitude longer. In recent years, Tc-99m has become readily available in hospitals through the use of selective elution from a so-called molybdenum-99 (Mo-99) generator. The isotope Mo-99 produces Tc-99m as a radioactive decay product. (See for example, *Jackson et al*, U.S. Patent 4,031,198, column 1).

The lack of efficacious 99m-Tc myocardial imaging agents is probably the most important problem facing nuclear medicine today. Agents capable of visualizing myocardial infarcts would be especially useful in the clinic. There are two types of myocardial imaging agents: 1) The "positive" agents which accumulate in the infarcted area and therefore visualize the infarct as a "hot" spot of radioactivity on a relatively "cold" background of normal tissue. There are several "positive" 99m-Tc agents in current use, including 99m-Tc-pyrophosphate and 99m-Tc-HEDP; (*Poe, N.D.*, *semin. Nucl. Med* 7, 7-14 (1977); (*Buja, L.M. et al*, *J. Clin. Invest.* 60, 724-740 (1977); *Davis, M.A., et al*, *J. Nucl. Med.*, 17, 911-917 (1976); *Wakat, M.A., et al*, *ibid*, 21, 203-306 (1980)); 2) the "negative" agents which accumulate in the normal heart and therefore visualize the infarct as a "cold" area on a relatively "hot" background of normal tissue. There is currently no 99m-Tc "negative" imaging agent available. The agent used clinically is ^{201}Tl which is expensive, has a photo-peak that is low for optimum imaging, and provides a low count rate per dose. The replacement of ^{201}Tl with a 99m-Tc agent is a major quest in nuclear medicine.

The use of 99m-Tc radiopharmaceuticals for hepatobiliary imaging is well known in the art. By hepatobiliary imaging agent is meant a radiopharmaceutical which clears the bloodstream after a few minutes, accumulates in the liver and is subsequently secreted by the liver into the bile, gallbladder, common bile duct, and intestines. There has been a strong belief in the art that efficient hepatobiliary imaging agents have to be anionic. Thus, *Firnau* *European Journal of Nuclear Medicine*, vol. 1, 137-139 (1976) reviewed several references which disclose Tc-99m hepatobiliary imaging agents, and concluded that an absolute structural requirement for a substance to be excreted by the liver is that it be an organic anion. *Firnau* states that the reason for gallbladder and bile duct imaging in the Tc-99m chelates of the prior art, is their ability to quickly pass through the liver, this ability being rather unspecific and common to all organic anions.

This prejudice in the art towards the use of anionic lipophilic complexes of 99m-Tc appears to be borne out by other work in this area. *Loberg et al*, U.S. Patent 4,017,596 disclose liver-clearing chelates of 99m-Tc, wherein the chelating agents are substituted iminodiacetic acids and 8-hydroxyquinolines. These complexes are anionic. *Loberg et al* (*International Journal of Applied Radiation and Isotopes*, 1978, vol. 29, pp. 167-173) disclose technetium 99m-labeled N-(2,6-dimethylphenylcarbamoyl methyl)-iminodiacetic acid (Tc-HIDA) and its potential use as a radiopharmaceutical. *Loberg et al* (in Abstract: Society of Nuclear Medicine, 23rd Annual Meeting, 1976) demonstrate that this Tc-HIDA is an anionic monomer containing two HIDA ligands per Tc center. *Winchell et al*, U.S. Patent 3,928,552 disclose a hepatobiliary radiopharmaceutical comprising 2-mercaptoisobutyric acid, chelating reduced technetium-99m. The aforementioned review article by *Firnau* (*Eur. J. of Nuclear Medicine*, 1, 137-139 (1976)) indicates that this radiopharmaceutical of *Winchell et al* is anionic. *Jackson et al*, U.S. Patent 4,031,198 disclose a radiopharmaceutical for imaging the liver, labeled with technetium-99m, which includes a complexing agent which is a lipophilic mercaptan or thioketal. The mercaptan or thioketal complexes in this reference fall within the general type of anionic complexes discussed in the aforementioned *Firnau* review article.

Hunt et al, U.S. Patents 4,088,747 and 4,091,088 discuss phenolic aminocarboxylic acid-liganded radiopharmaceuticals of technetium-99m. These phenolate/carboxylate type of ligands are known to be anionic, and the resulting pharmaceuticals of 99m-Tc fall within the general type of the review article by

Firnau.

Thomas et al., in *Journal of the American Chemical Society*, vol. 101, n° 16 August 1, 1979, also disclose a technetium radiopharmaceutical which is a lipophilic anionic complex of technetium.

G.D. Robinson, Jr et al., in *Journal of Nuclear Medicine*, 1975 vol. 16, n° 6; *Proceedings of 22nd annual meeting*, pages 561—2, describe the brain uptake of Tc—99m—trifluoroacetylacetate which is not a cationic complex of technetium.

From this brief review of the prior art, it can be concluded that hepatobiliary imaging agents of technetium—99m currently in clinical use have an anionic character. Because of this property however, they all suffer from a serious deficiency. High levels of bilirubin reduce, or eliminate, the ability of anionic agents to image the hepatobiliary system. *Harvey, L. et al.*, *J. Nucl. Med.*, 20, 310—313 (1979) have recently shown that this is because bilirubin is also anionic and therefore at high concentrations, it blocks the anion clearance mechanism of the liver and prevents anionic imaging agents from accumulating in the liver. This is a serious clinical problem since many jaundiced patients, with obvious hepatobiliary malfunction, have high bilirubin levels and therefore cannot be successfully imaged with anionic agents.

Nora, U.S. Patent 4,058,593 provides the only example of a cationic radiopharmaceutical based on technetium—99m which accumulates, albeit to a very small extent, in the liver. *Nora* discloses bone-specific radiopharmaceuticals based on technetium—99m with a complexing agent selected from the group of stannous fluoride, metal trifluorostannate and metal pentafluorodistannate. These agents however, are not lipophilic, and act predominantly by mechanical deposition in the liver. The agents are not hepatobiliary imaging agents since they do not clear the liver and are not secreted therefrom into the bile, gallbladder, common bile duct, and intestines. Thus, the liver deposition observed by *Nora* would be insufficient to obtain good hepatobiliary imaging.

J.E. Fergusson et al. in *Australian Journal of Chemistry*, vol. 93, 1970, pages 453—61, in *Nature*, vol. 183, April 11, 1959, pages 1039—40 and in *Chemistry and Industry*, March 26, 1960, pages 347—348, describe complexes of Tc—(II), —(III) and —(IV) which exemplified new oxidation states of technetium. However, although some of these complexes are cationic complexes, no utility is suggested for these complexes.

A need therefore, continues to exist for myocardial imaging agents based on Tc—99m, especially so-called "negative" myocardial infarct imaging agents. A need also continues to exist for cationic complexes of Tc—99m which will deposit in the liver and will be secreted therefrom, thus providing efficient hepatobiliary imaging.

Disclosure of Invention

It is therefore an object of the invention to provide cationic lipophilic Tc—99m radiopharmaceuticals for use in nuclear medicine.

Another object of the invention is to provide cationic lipophilic complexes of Tc—99m having an n-octanol/saline partition coefficient greater than about 0.5, for hepatobiliary imaging, and for negative myocardial infarct imaging.

Still another object of the invention is to provide a diagnostic product for hepatobiliary myocardial, pancreas and brain imaging in a mammal comprising an imaging amount of a cationic lipophilic complex of Tc—99m.

A further object of the invention is to provide a process for the preparation of cationic lipophilic complexes of Tc—99m of the formula:



wherein L is a neutral lipophilic ligand which is strongly chelating towards a ^{99m}Tc cation and which is capable of reducing Tc^{+7} to a lower valence state; X are the same or different monovalent anionic ligands, which comprises:

reducing a $^{99m}Tc^{+7}$ species to a lower valency state species with a ligand L, wherein the $^{99m}Tc^{+7}$ is present in an aqueous phase, wherein the ligand L is present in a water immiscible phase in intimate contact with said aqueous phase, and wherein during the reduction, said lower valency state species of ^{99m}Tc is transferred to said non-aqueous phase.

Brief Description of the Drawings

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

Figure 1 shows a scanning photographic anterior image of a mongrel dog, 30 minutes post injection of ^{99m}Tc (diars) $_2Br_2^+$, where diars = o-phenylenebis (dimethylarsine).

Figure 2 is a schematic describing the photograph of Figure 1. Both the photograph and accompanying schematic were taken after the complex had cleared the blood (5 minutes after injection), entered the liver and started clearing the liver and entering the gallbladder (10 minutes after injection). The picture is taken at the time when the gallbladder has taken up the bulk of the complex and the liver contains relatively little activity (30 minutes).

Figure 3 compares the gallbladder uptake and heart clearing of ^{99m}Tc (diars) $_2Cl_2^+$ with that of

99m—Tc (diars)₂Br₂⁺. Time dependent myocardial and gallbladder distributions obtained by computer analysis of scintigraphic data show that the chlorine complex clears from the heart more rapidly than the bromine complex, and that the gallbladder handles these two agents differently.

Figure 4 shows the blood clearance curves for the two complexes of Figure 3. It is clear that these two chemically similar agents are somewhat differentiated in the biological system.

Best Mode for Carrying out the Invention

The present invention provides cationic lipophilic complexes of 99m—Tc for imaging in nuclear medicine. These complexes are useful for negative myocardial infarct imaging, for hepatobiliary imaging, for pancreas imaging, and potentially for the imaging of other organs, such as the brain, lungs, kidney and the like.

The complexes of the present invention are particularly useful for negative myocardial infarct imaging. These are the first 99m—Tc myocardial imaging agents which accumulate in the normal heart and visualize the infarct as a cold area on a relatively hot background of normal tissue. As such, they are an optimal replacement for 201—Tl⁺, the agent presently in use. They provide a rapid and safe diagnostic technique to determine if infarction has occurred, and to assess the extent and location of the disease. They show specificity for viable myocardial tissue relative to ischemic tissue, and non-viable myocardium, as well as surrounding organs. They rapidly clear from the blood in order to provide low background. Furthermore, by varying the chelating agent of the ^{99m}Tc center, it is possible to vary the rate of clearance of the complexes, and permit studies which are not possible with 201—Tl (e.g., serial scanning). 201—Tl clears at a specific, unique rate which cannot be varied.

The present invention also provides cationic lipophilic complexes of 99m—Tc as true hepatobiliary imaging agents. It has come as a great surprise to the present inventors to discover that cationic complexes of Tc—99m are capable of imaging the hepatobiliary system. This discovery goes against the general understanding and prejudice of the prior art. As stated previously, *Firnau* (Eur. J. of Nuclear Medicine, vol. 1, 137—139 (1976)) delineated the structural requirements for substances that serve as hepatobiliary imaging agents. Among them, it was believed that only organic anions would be able to quickly pass through the liver and image the gallbladder and bile ducts. Without being bound by any particular theory, Applicants believe that they have discovered that a cationic clearing mechanism of the liver is capable of clearing cationic lipophilic complexes of 99m—Tc. This directly contradicts the teachings of the prior art. The discovery of cationic imaging agents for the hepatobiliary system, opens up the possibility of treating patients with severe jaundice having high bilirubin levels, and which could heretofore not be imaged with the standard prior art anionic complexes.

By "cationic lipophilic complexes" is meant complexes of 99m—Tc having lipophilic ligands and an overall cationic charge. The cationic charge on the overall complex can be readily determined by evaluating its migration on an electrophoresis apparatus, or evaluating its absorption properties on cationic ion exchange resins or other absorption materials.

The term "lipophilic" as used in the invention implies that the ligands and complexes derived therefrom range from being purely lipophilic to having a balance of hydrophilic and lipophilic character. The term therefore encompasses solubilities which range from exclusive solubility in non-polar, water-immiscible organic solvents, to complexes having solubility both in these solvents and aqueous solvents. At the other extreme are the non-lipophilic or hydrophilic cationic complexes, which are soluble exclusively in aqueous or polar organic water miscible solvents. It has been discovered that the cationic, highly lipophilic complexes of Tc—99m are excellent hepatobiliary imaging agents, rapidly clearing the bloodstream and the liver and depositing in the gallbladder, bile ducts and intestines. On the other hand, lipophilic cationic complexes having a balance of lipophilicity and hydrophilicity, and being soluble both in aqueous and non-aqueous, non-polar solvents are excellent imaging agents for the myocardium. Purely hydrophilic cationic complexes of technetium 99m, on the other hand, do not show any hepatobiliary imaging properties; they are rapidly cleared through the kidney. In summary, the complexes of the present invention range from being purely lipophilic to having a balance of lipophilicity and hydrophilicity, the latter having solubility in water and in non-polar, water-immiscible solvents.

The gradation of lipophilicity of the complexes of the present invention can be established by reference to partition coefficients using n-octanol/water, or n-octanol/buffer, or n-octanol/saline (*King and Blau*, J. Nucl. Med., 21, 147—152 (1980); *Oldendorf, ibid*, 19, 1182 (1978) and *Proc. Soc. Exp. Biol. Med.*, 147, 813—816 (1974)). In general, those cationic lipophilic complexes of Tc—99m having n-octanol/saline partition coefficients greater than about 0.05 are useful in the present invention.

Among the preferred cationic lipophilic complexes of the invention are those having the formula:



In this formula, L represents a lipophilic ligand strongly chelating for a Tc—99m cation wherein both L's may be the same or different, and X is an easily replaceable monovalent anionic ligand, wherein the three X's may be the same or different.

L has the general formula:

wherein n=2—5, preferably 2 or 3;

wherein A represents an alkylene lipophilic radical, or a monocyclic or polycyclic cycloaliphatic or aromatic lipophilic radical which may optionally be heterocyclic by containing in the ring or rings thereof, an atom selected from the group consisting of N, O, P, S or B. Most preferably, A is a lower alkylene radical, or A is a monocyclic or polycyclic aromatic radical. A may further be substituted, when necessary to increase the hydrophilic character of the molecule, with water solubilizing neutral groups such as hydroxy groups, thiol groups, carbonyl groups, and the like.

Y: is a neutral functional group having a free electron pair, capable of complexing with a Tc—99m cation having oxidation states less than +VII, preferably ranging from +I to +V. Thus, Y: may either be Y¹R₂ or Y²R. Y¹ may be selected from the group consisting of N, P, As, Sb, or Bi. Y² can be selected from the group consisting of O, S, Se or Te. R is hydrogen or a C₁—C₁₅ straight or branched chain alkyl group. R may be unsubstituted or be substituted along or on the hydrocarbon chain with oxygens, nitrogens, sulfurs, or phosphorus, to thereby control the lipophilicity of the Tc—99m complex.

Among the preferred lipophilic ligands L are the following:

DMPE ((CH₃)₂P—CH₂CH₂—P(CH₃)₂);

diars (o—C₆H₄(As(CH₃)₂)₂);

diphos ((C₆H₅)₂P—CH₂CH₂—P(C₆H₅)₂);

tris (1-pyrazolyl)borato;

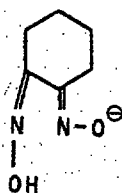
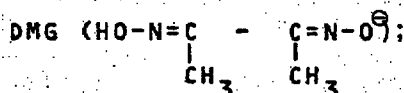
porphyrin;

tetraphos P(CH₂CH₂P(C₆H₅)₂)₃;

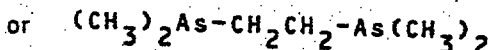
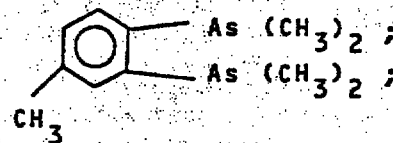
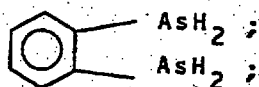
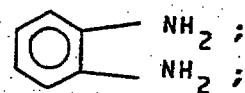
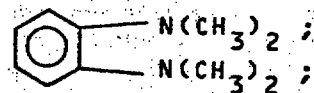
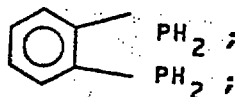
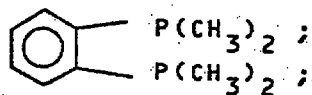
DAE ((C₆H₅)₂As—CH₂CH₂As(C₆H₅)₂);

DIEN (H₂N—CH₂CH₂NHCH₂CH₂NH₂);

PPN (RN(CH₂CH₂P(C₆H₅)₂)₂, where R=H unsubstituted C₁—C₁₅ alkyl; or C₁—C₁₅ alkyl, substituted by polar functional groups capable of rendering the resulting radical R with a wide range of hydrophilicity. A preferred series of Radicals R are those described in: Nozzo *et al*, J. Amer. Chem. Soc., 101 3683(1979) and Wilson *et al*, *ibid*, 100, 2269(1978), e.g.



H₂P—CH₂CH₂PH₂;
H₂N—CH₂CH₂—SH;
H₂As—CH₂CH₂—AsH₂;
H₂N—CH₂CH₂—NH₂;
HS—CH₂CH₂—SH;
(CH₃)₂N—CH₂CH₂—N(CH₃)₂;
tris (1-pyrazolyl)methane;



As mentioned above, any ligand which would render the final 99m—Tc complex lipophilic, works in the present invention. The final 99m—Tc complex may thus be soluble in solvents ranging from oil-soluble solvents such as aromatic hydrocarbons, aliphatic or cycloaliphatic hydrocarbons, halogenated hydrocarbons, and the like, to more polar non-aqueous solvents such as alcohols or ketones. Among the

aromatic hydrocarbons are benzene, toluene, xylenes, chlorobenzene, bromobenzene, and the like. Among the cycloaliphatic hydrocarbons are cyclopentane, cyclohexane, cyclooctane, etc. Among the halogenated hydrocarbons are chloroform, methylene chloride, carbon tetrachloride, ethylene dichloride, and the like. Among the ketones are acetone, methyl ethyl ketone and the like. As mentioned previously, the term

5 "lipophilic" as used in this invention, also includes solubility in both water and purely oil-soluble solvents. X is a monovalent ligand which may be selected for example, from the group consisting of F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- , or RS^- . The latter thiol derivatives are especially important since the R group can be varied for chain length, steric bulk, electronic nature, charge and lipophilicity, *vide supra*.

10 In the cation $[L_2 99mTc X_2]^+$, both X's taken together may be part of a bidentate ligand capable of bridging *cis* coordination sites in a Tc-99m cation. Such ligands would include oxalate, $HSCH_2CH_2SH$, $HSCH_2COOH$, $H_2N-CH_2CH_2-NH_2$, and other derivatives using liganding functional groups such as HO' , HS' , $COOH$, NH_2 , and the like. These ligands can also be substituted on the backbone to vary chain length, steric bulk, etc.

15 Among the preferred compounds for hepatobiliary or myocardial imaging are the 99m-Tc complexes derived from diars and tetraphos. The most preferred myocardial imaging agent is *trans*-99m-Tc $(DMPE)_2Cl_2^+$, and the most preferred hepatobiliary agent is $^{99m}Tc(tetraphos)Cl_2^+$.

The 99m-Tc lipophilic complexes of the present invention are prepared by novel techniques developed by the present inventors. Because of their short life (physical half-life of Tc-99m is 6 hours), the complexes must be manufactured near the place of use. The 99m-Tc isotope is produced by radioactive decomposition of its mother isotope, molybdenum Mo-99. The isolation of the daughter isotope is in practice carried out with the aid of the so-called radionuclide generators, directly at the place where the material is to be used. The mother isotope, for example sodium molybdate or ammonium molybdate, is adsorbed on an adsorption column on a suitable carrier material, such as aluminum oxide, zirconium hydroxide or silica gel; the daughter isotope can be eluted by means of a suitable eluent and thus be separated from the mother isotope. When using a Mo-99 generator, the daughter isotope Tc-99m is eluted, for example, as pertechnetate (TcO_4^-) by means of physiological sodium chloride solution. The pertechnetate is then reduced from the +VII level to a lower valency level, preferably +I to +V, most preferably +III level, *infra*.

Normally, the eluates obtained from the generator and the solutions of derivatives which may subsequently be produced have a relatively low specific activity per volume (Tc-99m < 5mCi/ml), though this suffices for static scintigraphy. For dynamic studies, to follow rapid functional sequences and for sequence scintigraphy, it is necessary to administer a high activity in as small a volume as possible. The detectors used are so-called scintillation cameras in combination with film recording or magnetic tape recording and computer evaluation. The specific activity per volume should be at least 10 to 15mCi/ml. To prepare such high specific activity solutions, different prior art methods can be used:

35 1) The use of Mo-99-Tc-99m generators of high activity concentration (300-500 mCi). On fractional elution, these generators give, within the first few days, pertechnetate eluates of adequate specific activity per volume, namely 10-15 mCi/ml. Upon preparation of reduced derivatives thereof, the specific activity per volume decreases due to dilution (Benes, U.S. Patent 3,961,038, column 2);

40 2) Extraction of an Mo-99/Tc-99m solution with methyl ethyl ketone, evaporation of solvent and solution of the residue in physiological sodium chloride solution (Journal of Nuclear Medicine, 11, 386 (1970));

3) Contact of an aqueous solution of a 99m-Tc radionuclide of low specific activity with a metal hydroxide precipitate, separation of the precipitate with the radionuclide concentrated therein, and solution of the precipitate in an aqueous solution of a chelating agent (Benes, U.S. Patent 3,961,038).

45 As mentioned above, Tc-99m is obtained from the generators in the form of a pertechnetate which has a relatively long dwelling time in human organs and because of this excessively long "biological half-life" is unsuitable for diagnostic applications. To manufacture the lipophilic complexes of the present invention, the pertechnetate is reduced. A number of reducing agents can be used for this purpose, and these are well known in the art. These reducing agents may include ascorbic acid, preferably in the presence of iron ions, sodium borohydride, Sn(II), or the use of the lipophilic chelating agent as the reducing agent *per se*. Other reducing metals such as ferrous, chromous, titanous and zirconyl ions can be used.

50 The essential aspects of the preparative methods developed by the present invention however, relate to a) the complexation reaction of the lipophilic ligand on the 99m-Tc nucleus itself and b) purification of the complex.

55 A) *Complexation Reaction*. Because the pertechnetate or reduced derivative thereof (prepared by using one of the aforementioned reducing agents) is normally water soluble, and both the lipophilic ligand and final 99m-Tc complex may not be water soluble, it may be necessary to carry out the complexation reaction in a biphasic system.

60 When the ligand and final product are water soluble however, such a biphasic system is not necessary.

When using the biphasic system, the technetium starts out in the aqueous phase (as it is obtained from the Mo-99 generator) and is extracted into the non-aqueous phase during the preparation. The non-aqueous phase is necessary to dissolve the final product. Such biphasic complexation reactions can be carried out in a non-stirred or well-stirred condition. In the former case, the complexation reaction occurs at the interface and the final product diffuses into the non-aqueous phase. In the latter system, the reaction

occurs in an "emulsion" with the product concentrating in the non-aqueous droplets. Any non-aqueous, water immiscible solvent may be used for such a biphasic complexation reaction. The previously listed water immiscible solvents (hydrocarbons and the like) are most preferred. The non-aqueous solvent should be capable of dissolving the lipophilic ligand used as starting material, and be capable of dissolving the final cationic lipophilic complex of Tc-99m. It should be easily separable from an aqueous solution by a standard separatory funnel-type separation. The final product should be easily obtainable therefrom by, for example, evaporation of the solvent.

The complexation reaction either in monophasic or biphasic systems, is carried out so that a large stoichiometric excess of lipophilic ligand is utilized over the stoichiometric amount of Tc-99m plus Tc99, present in the pertechnetate state or reduced state. Preferably, more than a tenfold excess of lipophilic ligand over 99m-Tc + 99Tc is used.

The reaction is carried out over a wide range of temperatures, with a proviso that the aqueous phase (and non-aqueous phase, if used) should remain liquid throughout the preparation. Thus, temperatures in the range of 0-80°C are normally used, most preferably 10-50°C.

The reaction times range from a few minutes to 1-2 hours. It should be recalled that the half-life of Tc-99m is only 6 hours and the reaction times have to be adjusted accordingly.

B) *Isolation and Purification of the Cationic Lipophilic Complexes.* If a biphasic system is used, and after the reaction has come to a substantial completion, the aqueous phase and the non-aqueous phase are separated by standard physical methods such as utilization of a separatory funnel. It is possible at this stage to add excess non-aqueous solvent either of the same or different type than that used for the reaction, to further extract the aqueous phase. All non-aqueous phases are then combined and, if necessary the volume is reduced to a manageable level. The non-aqueous phase is then loaded on a chromatographic system which will adsorb cations and which is capable of separating cationic complexes from neutral or anionic molecules. In this manner, the cationic lipophilic complex of Tc-99m is adsorbed on the chromatographic material and purified from neutral unreacted ligand, or any other neutral or anionic impurity. When a single phase is used, the whole preparation can normally be loaded (after dilution) on the chromatographic material.

Among the preferred materials used for chromatography are alumina, silica, cationic exchange resins (styrene-based, cellulose-based, sugar-based, etc.), polyamide resins, cellulose resins, starch gel, and the like. After extensive washing with a non-eluting solvent, the cationic lipophilic complex is normally eluted with a polar organic solvent such as an alcohol, an amide, a ketone, or the like. For somewhat less lipophilic complexes, ion exchange chromatography is the most preferred method of purification.

After purification, as described above, the cationic lipophilic complex of Tc-99m is separated from the elution solvent if necessary, by rapid evaporation thereof. The complex is then dissolved or suspended in an appropriate pharmacologically acceptable administration medium.

Among the standard administration media, it is possible to use a vehicle which is saline, or 50/50 ethanol/saline (intravenous injection); vehicles wherein the concentration of ethanol is varied; vehicles wherein ethanol is replaced by other organic portions such as propylene glycol, glycerol, or dimethyl sulfoxide; or vehicles based on solubilization of the radiopharmaceutical in micelles. Nonionic surfactant emulsifying agents such as Tweens[®] can be used in administering water insoluble radiopharmaceuticals (Risch et al in "The Chemistry of Radiopharmaceuticals", New York, Masson Publishers, 1978, pp. 123-154). Another method is to administer the complexes suspended or dispersed in water or aqueous solutions. This could be accomplished by dispersing the compounds *via* sonication, for example.

It is preferred to administer the radiopharmaceutical in a radioactive dose of from 0.01 mCi/ml to 10 mCi/ml, most preferably 2 mCi/ml - 5 mCi/ml. The administration dose by weight of animal is 0.001 mCi/kg - 1 mCi/kg; preferably 0.002 mCi/kg - 0.1 mCi/kg.

Imaging of the myocardium or the hepatobiliary system can then be carried out (after waiting for appropriate periods of time to permit blood clearance of the radiopharmaceutical), by standard scanning techniques (Andres, J. T. et al, "Nuclear Medicine", Wiley & Sons, N.Y., 1977; "Basic Science Principles of Nuclear Medicine", Boyd, C.M. and Dalrymple, G.V., eds., Morby, St. Louis, 1974). For example, time dependent scintiscans of the chest region of a patient can be used. A computer interface, 16 crystal, Ohio Nuclear Spectrometer, is used for these scans and about 5 mCi of a given radiopharmaceutical is injected; blood samples are concurrently collected via an indwelling intravenous catheter in order to determine blood clearance rates. Time dependent tissue distribution studies are then conducted.

The present complexes used for imaging the myocardium and the hepatobiliary system lend themselves to ready preparation, in a form which is compatible with a "kit" synthesis. A standardized kit preparation may involve a kit comprising a carrier being compartmented to receive a series of containers (vials; open ended tubes with or without stopper means at one or both ends; small bottles; and the like) in close confinement wherein one of the containers contains a 99mTc source, e.g. a standard Mo-99 molybdenum generator, and one or more containers might contain the particular lipophilic ligand by itself, or in combination with an appropriate reducing agent. These materials may be dissolved in an appropriate solvent or be provided solvent-free, with specific instructions. Pertechnetate from the generator is transferred into a container containing the ligand (and reductant, if one is used); after mixing and reaction for the specified time, the mixture is then passed through the appropriate chromatographic material having adsorbing capacity for cations. This material can be present in a third container which container is in the

form of a short open ended chromatographic column; after passage therethrough, the ^{99m}Tc cationic complexes become absorbed on the chromatographic material. After rinsing with appropriate wash solvent, a displacement solution is then passed through the column to elute the desired radiopharmaceutical. In a preferred embodiment, such a kit would comprise a syringe fitted with a short cylindrical adapter capable of maintaining chromatographic material between the barrel of said syringe and the needle of said syringe (available commercially). This adapter contains the chromatographic material having adsorbing capacity for cations. After complexing the ligand on the ^{99m}Tc center (with con-comitant reduction), the mixture is introduced into the barrel of the syringe. The mixture is ejected through the adapter containing the chromatographic material; the syringe is reloaded with wash solution which is ejected through the adapter; the syringe is then reloaded with displacement solution which is ejected through the adapter, removing the radiopharmaceutical into an appropriate container.

Preparations with such a kit may be completed anywhere between 15 minutes and 2 hours, thus making it a readily available and easily manageable procedure.

Having now generally described this invention, the same will be better understood by reference to specific examples, which are included herein for purposes of illustration only and are not intended to be limiting thereof.

Example 1

Preparation of $\text{trans-[Tc-}^{99m}\text{(diars)}_2\text{Br}_2\text{]Br}$

10 ml of an aqueous alcoholic solution of HBr (a mixture of 6M HBr and 95% ethanol in equal volumes), 5.0 ml of ^{99m}Tc -sodium pertechnetate (obtained from a molybdenum generator and diluted to 5.0 ml with saline), and 0.01 ml of *ortho*-phenylenebis(dimethylarsine) were added to a 25 ml Erlenmeyer flask equipped with a Teflon[®]-coated stirring bar. The mixture was stirred and heated on a hot plate for 30 minutes. The mixture was allowed to cool for 20 minutes at room temperature. 10 ml of methylene chloride was added to the flask and stirred for 20 minutes. The organic phase was separated using a separatory funnel and loaded onto a 0.7 cm $\times$ 3.0 cm alumina adsorption column prepared with methylene chloride and topped off with 1 cm of sand. The column was washed with 4-6 ml of methylene chloride and the +1 species was eluted with 95% ethanol. The eluate was collected in 1 ml fractions. Approximate yield was 65%.

Example 2

Preparation of $^{99m}\text{Tc}(\text{DMPE})_2\text{Cl}_2\text{]Cl}$

The following were added to a 25 ml Erlenmeyer flask equipped with a Teflon[®]-coated stir bar: 10.0 ml of 0.1 N aqueous alcoholic HCl, 0.5 ml of $\text{Na}^{99m}\text{TcO}_4$, and 0.05 ml of DMPE (Bis(1, 2-dimethylphosphino)ethane). The mixture was stirred and heated at a boil for 30 minutes. After 15 minutes of stirring and heating, 5 drops of 3 M HCl were added to the flask. The mixture was cooled at room temperature for 15 minutes; it was then diluted to a volume of 50 ml with distilled water and loaded onto a SP-Sephadex C-25[®] ion exchange column (1.5 cm I.D. $\times$ 7.0 cm) prepared with distilled water and layered with 1 cm of sand. The column was washed with 50 ml of distilled water and the cationic species subsequently eluted with normal saline. Yield is approximately 65%.

Example 3

Preparation of $^{99m}\text{Tc}(\text{DMPE})_2\text{Br}_2\text{]Br}$

The same procedure was followed as for Example 2, except for the following changes:
 (1) 0.1 N aqueous alcoholic HBr instead of HCl;
 (2) 30 drops of 3 M HBr were added after 15 min., instead of 5 drops of 3 M HCl;
 (3) diluted to a total volume of 150 ml instead of 50 ml before loading onto the column;
 (4) column: 1.5 cm I.D. $\times$ 10.0 cm;
 (5) Yield was approximately 47%

Example 4

Myocardial Imaging with $\text{trans-[Tc}(\text{diars})_2\text{Br}_2\text{]Br}$

A normal mongrel dog was injected using a 50% ethanol/50% saline mixture as vehicle with the diars complex prepared in Example 1. Images of the dog were obtained with a high sensitivity colimator clearly visualizing the myocardium, with maximal myocardial uptake occurring about 20 minutes post injection. The bulk of the activity is taken out by the hepatobiliary system. Table 1, further shows the tissue distribution studies using normal female Sprague-Dawley rats.

TABLE 1

		Time post dose			
		10 min	30 min	60 min	120 min
5	Blood	0.38(3)*	0.27(3)	0.21(1)	0.18(3)
	Heart	2.3(5)	1.8(1)	1.3(1)	1.0(1)
	Liver	4.5(6)	2.9(6)	2.7(3)	2.1(2)
	Pancreas	1.0(3)	1.2(2)	0.9(1)	0.8(1)
	Kidney	3.1(6)	2.3(1)	2.1(1)	1.9(1)
10	Femur Muscle	0.22(6)*	0.29(3)	0.26(5)	0.28(2)

15 *Standard deviation of last significant digit given in parentheses.

The Table demonstrates that normal rats show significant myocardial uptake (2.3% of the dose/g in myocardium at 10 minutes post injection).

20 **Example 5**
Myocardial Imaging Using $[99m\text{-Tc}(\text{DMPE})_2\text{Br}_2]^+$

Myocardial uptake by the heart of a normal mongrel dog was observed with the title complex, under the same conditions as those for Example 4.

25 **Example 6**
Hepatobiliary Imaging Using $\text{trans-[Tc-99m}(\text{diars})_2\text{Br}_2]\text{Br}$

The title complex was injected in the same vehicle as in Example 4 into a mongrel dog and images were obtained by positioning a camera directly over the chest of the dog. The following results were obtained.

30 0 minutes: Immediately after injection, most of the complex is in the blood pool which is predominantly in the heart chambers.

1 minute: One minute after injection, the complex begins to clear from the blood and starts to enter the liver. The gallbladder does not yet contain any activity.

5 minutes: The complex is all gone from the blood, the heart image has disappeared, and most of it is in the liver. A small amount has begun to enter the gallbladder.

35 10 minutes: The gallbladder has taken up most of the complex and appears brighter than even the liver.

20 minutes: The gallbladder has taken up the bulk of the complex and the contains relatively little activity. Figures 1 and 2 demonstrate the image obtained after 30 minutes.

40 **Example 7**
Comparison Between the Use of $99m\text{-Tc}(\text{diars})_2\text{Br}_2^-$ and $99m\text{-Tc}(\text{diars})_2\text{Cl}_2^-$ as hepatobiliary and Myocardial Imaging Agents

The two title complexes were injected into a dog as described for the complex of Example 4. Whereas with $99m\text{-Tc}(\text{diars})_2\text{Br}_2^-$, the myocardium is readily visualized 20-40 minutes post intravenous injection, and gallbladder uptake is relatively slow, with the very similar complex $99m\text{-Tc}(\text{diars})_2\text{Cl}_2^-$, the myocardium is imaged to a somewhat lesser degree and gallbladder uptake is rapid. These differences are graphically illustrated in Figure 3, wherein are plotted time dependent myocardial and gallbladder distributions obtained by computer analysis of scintigraphic data; data for a given complex are normalized, but comparative data between complexes are not. From Figure 3, it is seen that $99m\text{-Tc}(\text{diars})_2\text{Cl}_2^-$ clears from the heart much more rapidly than $99m\text{-Tc}(\text{diars})_2\text{Br}_2^-$ and that the gallbladder handles these two agents differently. Blood clearance curves for these two complexes are shown in Figure 4, and again it is clear that these two chemically similar agents although being excellent imaging agents are biologically differentiated.

55 **Claims for the Contracting States: BE CH DE FR GB IT LI NL SE**

1. A cationic lipophilic complex of Tc-99m having an n-octanol/saline partition coefficient greater than about 0.05.

2. The complex of Claim 1, which is soluble in non-polar water immiscible solvents.

3. The complex of Claim 2, which is also soluble in polar water-miscible solvents.

4. The complex of Claim 1, which has the formula



TABLE 1

	Time post dose				
	10 min	30 min	60 min	120 min	
Blood	0.38(3)*	0.27(3)	0.21(1)	0.18(3)	
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Kidney	3.1(6)	2.3(1)	2.1(1)	1.9(1)	
Femur Muscle	0.22(6)	0.29(3)	0.26(5)	0.28(2)	

*Standard deviation of last significant digit given in parentheses.

The Table demonstrates that normal rats show significant myocardial uptake (2.3% of the dose/g in myocardium at 10 minutes post injection).

Example 5

Myocardial Imaging Using $[^{99m}\text{Tc}(\text{DMPE})_2\text{Br}_2]^+$

Myocardial uptake by the heart of a normal mongrel dog was observed with the title complex, under the same conditions as those for Example 4.

Example 6

Hepatobiliary Imaging Using $\text{trans-}[^{99m}\text{Tc}(\text{diars})_2\text{Br}_2]\text{Br}$

The title complex was injected in the same vehicle as in Example 4 into a mongrel dog and images were obtained by positioning a camera directly over the chest of the dog. The following results were obtained.

0 minutes: Immediately after injection, most of the complex is in the blood pool which is predominantly in the heart chambers.

1 minute: One minute after injection, the complex begins to clear from the blood and starts to enter the liver. The gallbladder does not yet contain any activity.

5 minutes: The complex is all gone from the blood, the heart image has disappeared, and most of it is in the liver. A small amount has begun to enter the gallbladder.

10 minutes: The gallbladder has taken up most of the complex and appears brighter than even the liver.

20 minutes: The gallbladder has taken up the bulk of the complex and the contains relatively little activity. Figures 1 and 2 demonstrate the image obtained after 30 minutes.

Example 7

Comparison Between the Use of $^{99m}\text{Tc}(\text{diars})_2\text{Br}_2^-$ and $^{99m}\text{Tc}(\text{diars})_2\text{Cl}_2^+$ as hepatobiliary and Myocardial Imaging Agents

The two title complexes were injected into a dog as described for the complex of Example 4. Whereas with $^{99m}\text{Tc}(\text{diars})_2\text{Br}_2^-$, the myocardium is readily visualized 20–40 minutes post intravenous injection, and gallbladder uptake is relatively slow, with the very similar complex $^{99m}\text{Tc}(\text{diars})_2\text{Cl}_2^+$, the myocardium is imaged to a somewhat lesser degree and gallbladder uptake is rapid. These differences are graphically illustrated in Figure 3, wherein are plotted time dependent myocardial and gallbladder distributions obtained by computer analysis of scintigraphic data; data for a given complex are normalized, but comparative data between complexes are not. From Figure 3, it is seen that $^{99m}\text{Tc}(\text{diars})_2\text{Cl}_2^+$ clears from the heart much more rapidly than $^{99m}\text{Tc}(\text{diars})_2\text{Br}_2^-$ and that the gallbladder handles these two agents differently. Blood clearance curves for these two complexes are shown in Figure 4, and again it is clear that these two chemically similar agents although being excellent imaging agents are biologically differentiated.

Claims for the Contracting States: BE CH DE FR GB IT LI NL SE

1. A cationic lipophilic complex of Tc-^{99m} having an n-octanol/saline partition coefficient greater than about 0.05.
2. The complex of Claim 1, which is soluble in non-polar water immiscible solvents.
3. The complex of Claim 2, which is also soluble in polar water-miscible solvents.
4. The complex of Claim 1, which has the formula



wherein L is a polyvalent neutral lipophilic ligand which is strongly chelating towards a ^{99m}Tc cation; X are the same or different monovalent anionic ligands; or, in the formula $(\text{L}_2^{99m}\text{TcX}_2)^+$, both X's are part of the same bidentate ligand capable of coordinating the *cis* positions of a ^{99m}Tc cation.

5. The complex of Claim 4, wherein L has the formula



wherein $n=2-5$;

wherein A is selected from the group consisting of a substituted or unsubstituted alkylene radical, a homomonocyclic or homopolycyclic lipophilic organic radical, and a heteromonocyclic or heteropolycyclic organic radical containing in at least one ring thereof an atom selected from the group consisting of N, O, P, S, or B;

Y: are the same or different neutral functional groups having a free electron pair capable of complexing with a ^{99m}Tc cation.

6. The complex of Claim 5, wherein $n=2$ or 3.

7. The complex of Claim 5, wherein A is $—\text{CH}_2\text{CH}_2—$.

8. The complex of Claim 5, wherein Y: are the same or different functional groups selected from the group consisting of Y^1R_2 and Y^2R wherein

Y^1 is an atom selected from the group consisting of N, P, As, Sb, and Bi;

Y^2 is an atom selected from the group consisting of O, S, Se, and Te; and

R is selected from the group consisting of hydrogen, an unsubstituted $\text{C}_1—\text{C}_{15}$ straight or branched chain alkyl group, and a $\text{C}_1—\text{C}_{15}$ straight or branched chain alkyl group substituted along or on the hydrocarbon chain with oxygen, nitrogen, sulfur or phosphorus.

9. The complex of Claim 5, wherein said ligands X's are the same or different ligands selected from the group consisting of F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- , and RS^- , wherein

R is selected from the group consisting of an unsubstituted $\text{C}_1—\text{C}_{15}$ straight or branched alkyl group, and $\text{C}_1—\text{C}_{15}$ straight or branched chain alkyl group substituted along or on the hydrocarbon chain with oxygen, nitrogen, sulfur or phosphorus.

10. The complex of Claim 4, wherein L is selected from the group consisting of:

DMPE $((\text{CH}_3)_2\text{P}—\text{CH}_2\text{CH}_2—\text{P}(\text{CH}_3)_2)$;

diars $(\text{o}-\text{C}_6\text{H}_4(\text{As}(\text{CH}_3)_2))$;

diphos $((\text{C}_6\text{H}_5)_2\text{P}—\text{CH}_2\text{CH}_2—\text{P}(\text{C}_6\text{H}_5)_2)$;

tris (1-pyrazolyl)borate;

porphyrin;

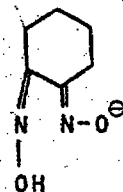
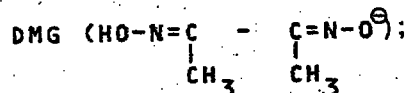
tetraphos $(\text{P}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_3)$;

DAE $((\text{C}_6\text{H}_5)_2\text{As}—\text{CH}_2\text{CH}_2\text{As}(\text{C}_6\text{H}_5)_2)$;

DIEN $(\text{H}_2\text{N}—\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2)$;

PPN $(\text{RN}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_2)$, where R=H or $\text{C}_1—\text{C}_{15}$

substituted or unsubstituted alkyl;



$\text{H}_2\text{P}—\text{CH}_2\text{CH}_2\text{PH}_2$;

$\text{H}_2\text{N}—\text{CH}_2\text{CH}_2—\text{SH}$;

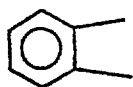
$\text{H}_2\text{As}—\text{CH}_2\text{CH}_2—\text{AsH}_2$;

$\text{H}_2\text{N}—\text{CH}_2\text{CH}_2—\text{NH}_2$;

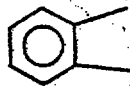
$\text{HS}—\text{CH}_2\text{CH}_2—\text{SH}$;

$(\text{CH}_3)_2\text{N}—\text{CH}_2\text{CH}_2—\text{N}(\text{CH}_3)_2$;

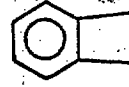
tris (1-pyrazolyl)methane;



$\text{P}(\text{CH}_3)_2$;
 $\text{P}(\text{CH}_3)_2$;

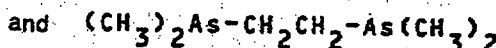
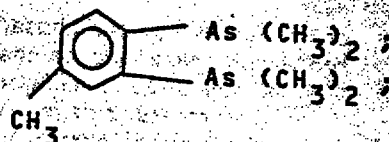
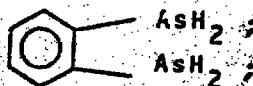
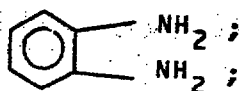


PH_2 ;
 PH_2 ;

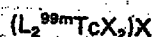


$\text{N}(\text{CH}_3)_2$;
 $\text{N}(\text{CH}_3)_2$;





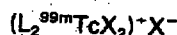
11. The complex of Claim 10, wherein L is selected from the group consisting of diars, DMPE and tetraphos.
 12. The complex of Claim 1, which is selected from the group consisting of $(^{99\text{m}}\text{Tc}(\text{diars})_2\text{Br}_2)\text{Br}$ and $(^{99\text{m}}\text{Tc}(\text{diars})_2\text{Cl}_2)\text{Cl}$.
 13. The complex of Claim 1, which is selected from the group consisting of $(^{99\text{m}}\text{Tc}(\text{DMPE})_2\text{Br}_2)\text{Br}$ and $(^{99\text{m}}\text{Tc}(\text{DMPE})_2\text{Cl}_2)\text{Cl}$.
 14. The complex of Claim 1, which is $(^{99\text{m}}\text{Tc}(\text{tetraphos})\text{Br}_2)\text{Br}$.
 15. The complex of any of claims 12—14, which is in the trans configuration.
 16. The complex of Claim 1 in combination with a pharmacologically inert vehicle.
 17. The complex of Claim 16, wherein said vehicle is 50:50 ethanol/saline.
 18. A process of preparing a cationic lipophilic complex of $^{99\text{m}}\text{Tc}$ of the formula:



- wherein L is a neutral lipophilic ligand which is strongly chelating towards a $^{99\text{m}}\text{Tc}$ cation and which is capable of reducing Tc^{+7} to a lower valence state;
 X are the same or different monovalent anionic ligands, which comprises:
 reducing a $^{99\text{m}}\text{Tc}^{+7}$ species to a lower valency state species with a ligand L, wherein the $^{99\text{m}}\text{Tc}^{+7}$ is present in an aqueous phase, wherein the ligand L is present in a water immiscible phase in intimate contact with said aqueous phase, and wherein during the reduction, said lower valency state species of $^{99\text{m}}\text{Tc}$ is transferred to said non-aqueous phase.
 19. The process of Claim 18, wherein, after said transfer of said lower valency state species of $^{99\text{m}}\text{Tc}$ into said water immiscible phase, the process further comprises:
 absorbing said species in complexation with said ligand L, on a material having adsorbing capacity for cations, being capable of separating cationic complexes from neutral or anionic molecules and eluting substantially pure $(^{99\text{m}}\text{TcL}_2\text{X}_2)^+$ species therefrom.
 20. A kit comprising a carrier being compartmented to receive a series of containers in close confinement which comprises:
 a first container containing a source of $^{99\text{m}}\text{Tc}$;
 a second container containing a polyvalent neutral lipophilic ligand L which is strongly chelating towards a $^{99\text{m}}\text{Tc}$ cation and able to form with this $^{99\text{m}}\text{Tc}$ cation a cationic lipophilic complex having an n-octanol/saline partition coefficient greater than about 0.05; and a third container containing chromatographic material having adsorbing capacity for cations.
 21. The kit of Claim 20, wherein said second container further contains a reducing agent capable of reducing $^{99\text{m}}\text{Tc}$ from a valency state of +VII to a lower valency state.
 22. The kit of Claim 20, wherein said third container is in the form of a short chromatography tube.
 23. The kit of Claim 20, wherein said third container is in the form of a syringe adapter capable of maintaining chromatographic material between the barrel of said syringe and the needle of said syringe.
 24. The kit of Claim 23, wherein said kit also contains a syringe capable of fitting said adapter.
 25. The kit of Claim 20, wherein said chromatographic material is selected from the group consisting of alumina, silica and a cationic exchange resin.
 26. The kit of Claim 20, wherein said $^{99\text{m}}\text{Tc}$ generator is a Mo—99 molybdenum generator.
 27. Diagnostic product for hepatobiliary, myocardial, pancreas and brain imaging in a mammal comprising an imaging amount of a cationic lipophilic complex of $\text{Tc}-^{99\text{m}}$ according to anyone of claims 1 to 17.

55 Claims for the Contracting State: AT

1. A process of preparing a cationic lipophilic complex of $^{99\text{m}}\text{Tc}$ of the formula:



- wherein L is a neutral polyvalent lipophilic ligand which is strongly chelating towards a $^{99\text{m}}\text{Tc}$ cation and which is capable of reducing Tc^{+7} to a lower valence state; X are the same or different monovalent anionic ligands, or, in the formula $(\text{L}_2^{99\text{m}}\text{TcX}_2)^+$, both X's are part of the same bidentate ligand capable of coordinating the cis positions of a $^{99\text{m}}\text{Tc}$ cation, which comprises:
 reducing a $^{99\text{m}}\text{Tc}^{+7}$ species to a lower valency state species with a ligand L, wherein the $^{99\text{m}}\text{Tc}^{+7}$ is



present in an aqueous phase, wherein the ligand L is present in a water immiscible phase in intimate contact with said aqueous phase, and wherein during the reduction, said lower valency state species of ^{99m}Tc is transferred to said non-aqueous phase.

2. The process of claim 1, wherein, after said transfer of said lower valency state species of ^{99m}Tc into said water immiscible phase, the process further comprises:

absorbing said species in complexation with said ligand L, on a material having adsorbing capacity for cations, being capable of separating cationic complexes from neutral or anionic molecules and eluting substantially pure $(^{99m}\text{TcL}_2\text{X}_2)^+$ species therefrom.

3. The process of claims 1 or 2, wherein the cationic lipophilic complex of Tc-^{99m} has an n-octanol saline partition coefficient greater than about 0.05.

4. The process of claims 1 or 2, wherein the cationic lipophilic complex of ^{99m}Tc is soluble in non-polar water immiscible solvents.

5. The process of claim 4, wherein the cationic lipophilic complex of ^{99m}Tc is also soluble in polar water miscible solvents.

6. The process of claim 1, wherein L has the formula:



wherein $n = 2-5$;

- wherein A is selected from the group consisting of a substituted or unsubstituted alkylene radical, a homomonocyclic or homopolycyclic lipophilic organic radical, and a heteromonocyclic or heteropolycyclic organic radical containing in at least one ring thereof an atom selected from the group consisting of N, O, P, S, or B;

Y: are the same or different neutral functional groups having a free electron pair capable of complexing with a ^{99m}Tc cation.

7. The process of claim 6, wherein $n = 2$ or 3.

8. The process of claim 6, wherein A is $-\text{CH}_2\text{CH}_2-$.

9. The process of claim 6, wherein Y: are the same or different functional groups selected from the group consisting of Y^1R_2 and Y^2R , wherein

Y^1 is an atom selected from the group consisting of N, P, As, Sb, and Bi;

- Y^2 is an atom selected from the group consisting of O, S, Se, and Te; and

R is selected from the group consisting of hydrogen, an unsubstituted C_1-C_{15} straight or branched chain alkyl group, and a C_1-C_{15} straight or branched chain alkyl group substituted along or on the hydrocarbon chain with oxygen, nitrogen, sulfur or phosphorus.

10. The process of claim 6, wherein said ligands X's are the same or different ligands selected from the group consisting of F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- , and RS^- , wherein

R is selected from the group consisting of an unsubstituted C_1-C_{15} straight or branched alkyl group, and C_1-C_{15} straight or branched chain alkyl group substituted along or on the hydrocarbon chain with oxygen, nitrogen, sulfur or phosphorus.

11. The process of claim 4, wherein L is selected from the group consisting of:

- DMPE $(\text{CH}_3)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{CH}_3)_2$;

diars $(\text{o-C}_6\text{H}_4(\text{As}(\text{CH}_3)_2))_2$;

diphos $((\text{C}_6\text{H}_5)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{C}_6\text{H}_5)_2)$;

tris (1-pyrazolyl)borate;

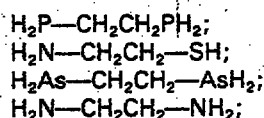
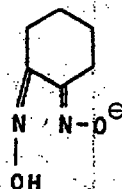
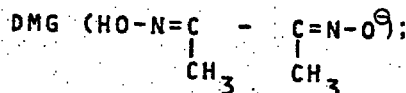
porphyrin;

- tetraphos $(\text{P}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_3)$;

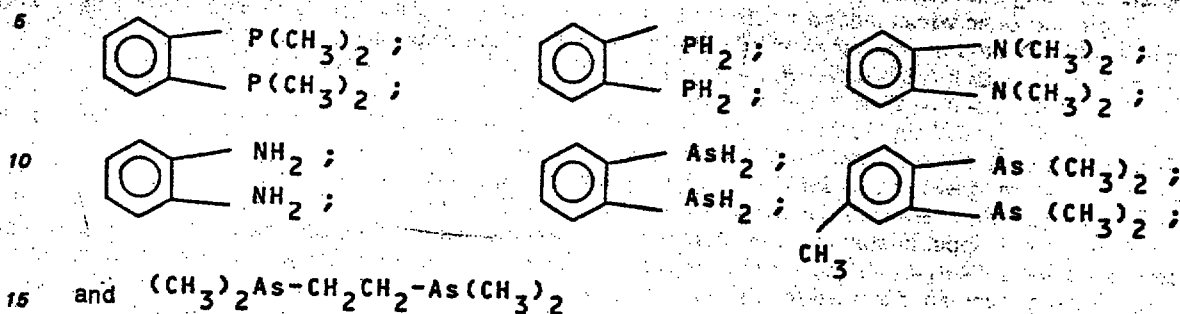
DAE $((\text{C}_6\text{H}_5)_2\text{As}-\text{CH}_2\text{CH}_2\text{As}(\text{C}_6\text{H}_5)_2)$;

DIEN $(\text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2)$;

PPN $(\text{RN}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_2)$, where R = H or C_1-C_{15} substituted or unsubstituted alkyl;



HS-CH₂CH₂-SH;
(CH₃)₂N-CH₂CH₂-N(CH₃)₂;
tris (1-pyrazolyl)methane;



12. The Process of claim 11, wherein L is selected from the group consisting of diars, DMPE and tetraphos.
- 20 13. The process of claim 1, wherein the cationic lipophilic complex of ^{99m}Tc is (^{99m}Tc(diars)₂(Br₂)Br or (^{99m}Tc(diars)₂Cl₂)Cl.
14. The process of claim 1, wherein the cationic lipophilic complex of ^{99m}Tc is (^{99m}Tc(DMPE)₂(Br₂)Br or (^{99m}Tc(DMPE)₂Cl₂)Cl.
15. The process of claim 1, wherein the cationic lipophilic complex of ^{99m}Tc is (^{99m}Tc(tetraphos)(Br₂)Br.
- 25 16. The process of any of claims 12—15 wherein the cationic lipophilic complex of ^{99m}Tc is in the trans configuration.
17. A kit comprising a carrier being compartmented to receive a series of containers in close confinement which comprises:
- 30 a first container containing a source of ^{99m}Tc;
a second container containing a polyvalent neutral lipophilic ligand L which is strongly chelating towards a ^{99m}Tc cation and able to form with this ^{99m}Tc cation a cationic lipophilic complex having an n-octanol/saline partition coefficient greater than about 0.05; and
a third container containing chromatographic material having adsorbing capacity for cations.
18. The kit of claim 17, wherein said second container further contains a reducing agent capable of
- 35 reducing ^{99m}Tc from a valency state of +VII to a lower valency state.
19. The kit of claim 17, wherein said third container is in the form of a short chromatography tube.
20. The kit of claim 17, wherein said third container is in the form of a syringe adapter capable of maintaining chromatographic material between the barrel of said syringe and the needle of said syringe.
21. The kit of claim 20, wherein said kit also contains a syringe capable of fitting said adapter.
- 40 22. The kit of claim 17, wherein said chromatographic material is selected from the group consisting of alumina, silica and a cationic exchange resin.
23. The kit of claim 17, wherein said ^{99m}Tc generator is a Mo-99 molybdenum generator.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI NL SE

- 45 1. Kationischer, lipophiler Komplex von Tc-99m mit einem n-Octanol/Salzlösung-Verteilungskoeffizienten größer als etwa 0,05.
2. Komplex nach Anspruch 1, welcher in unpolaren, wasserunmischbaren Lösungsmitteln löslich ist.
3. Komplex nach Anspruch 2, welcher ebenfalls in polaren, wassermischbaren Lösungsmitteln löslich
- 50 ist.
4. Komplex nach Anspruch 1, welcher die Formel
- $$(L_2^{99m}TcX_2)^+ X^-$$
- besitzt, worin
- 55 L ein mehrwertiger, neutraler, lipophiler Ligand ist, welcher mit einem ^{99m}Tc-Kation stark cheliert, X gleiche oder verschiedene einwertige, anionische Liganden sind oder in der Formel (L₂^{99m}TcX₂)⁺ beide X Teil des gleichen zweizähligen Liganden sind, welcher in der Lage ist, die cis-Positionen eines ^{99m}Tc-Kations zu koordinieren.
5. Komplex nach Anspruch 4, worin L die Formel
- 60
- $$(A)-(Y)_n$$
- besitzt, worin
- n = 2 bis 5;
- worin
- 65 A gewählt wird aus der Gruppe, bestehend aus einem substituierten oder unsubstituierten Alkyl-



Y gleiche oder verschiedene neutrale, funktionelle Gruppen mit einem freien Elektronenpaar sind, welches in der Lage ist, mit einem ^{99m}Tc -Kation einen Komplex zu bilden.

7. Komplex nach Anspruch 5, worin A —CH₂CH₂— ist.

Gruppe, bestehend aus Y^1R_2 und Y^2R , sind, worin
10 Y^1 ein Atom, gewählt aus der Gruppe, bestehend aus N, P, As, Sb und Bi, ist, und Y^2 ein Atom, gewählt aus der Gruppe, bestehend aus O, S, Se und Te, ist und

Y^1 ein Atom, gewählt aus der Gruppe, bestehend aus N, P, As, Sb und Bi, ist,

15 gewählt wird.

9. Komplex nach Anspruch 5, worin die Liganden X gleiche oder verschiedene Liganden, gewählt aus der Gruppe, bestehend aus F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- und RS^- , sind, worin

9. Komplex nach Anspruch 5, worin die Liganden X gleiche oder verschiedene der Gruppe, bestehend aus F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- und RS^- , sind, worin R eine ungesättigte, unsubststituierte geradkettigen oder verzweigten Kohlenwasserstoffkette ist.

R aus der Gruppe, bestehend aus einer unsubstituierten, geradkettigen oder verzweigten kettigen C₁-C₁₅ Alkylgruppe und einer geradkettigen oder verzweigten kettigen C₁-C₁₅ Alkylgruppe, substituiert entlang oder am Ende mit einem Sauerstoff, Stickstoff, Schwefel oder Phosphor, gewählt wird.

20 an die Kohlenwasserstoffkette mit Sauerstoff, Stickstoff, Schwefel oder Phosphor, gewählt

10. Komplex nach Anspruch 4,
DMPE $((\text{CH}_3)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{CH}_3)_2)$;

Diars (o-C₆H₄(As(CH₃)₂);

Diphos $((C_6H_5)_2P-CH_2CH_2-P(C_6H_5)_2)$;

25 Tris(1-pyrazolyl)borat;

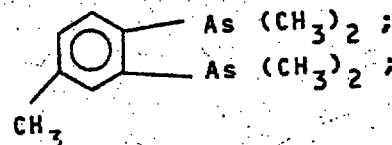
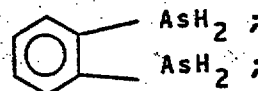
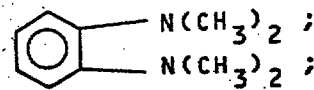
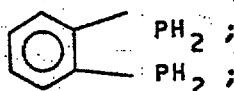
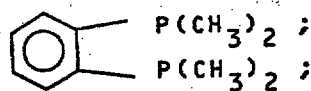
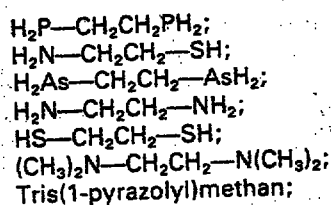
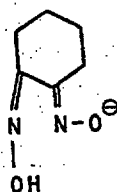
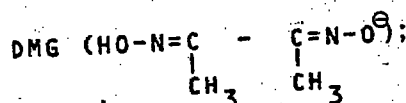
Protoporphyrin;

Tetraphos ($\text{P}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_3$);

DAE $((C_6H_5)_2As-CH_2CH_2As(C_6H_5)_2)$:

DIEN ($\text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2$);

30 PPN (RN(CH₂CH₂P(C₆H₅)₂)₂, worin R = H oder ein substituiertes oder unsubstituiertes C₁—C₁₅ Alkyl;



und $(\text{CH}_3)_2\text{As}-\text{CH}_2\text{CH}_2-\text{As}(\text{CH}_3)_2$

11. Komplex nach Anspruch 10, worin L aus der Gruppe, bestehend aus Diars, DMPE und Tetraphos,
65 gewählt wird.



12. Komplex nach Anspruch 1, welcher aus der Gruppe, bestehend aus $(^{99m}\text{Tc}(\text{Diars})_2\text{Br}_2)\text{Br}$ und $(^{99m}\text{Tc}(\text{Diars})_2\text{Cl}_2)\text{Cl}$, gewählt wird.
13. Komplex nach Anspruch 1, welcher aus der Gruppe, bestehend aus $(^{99m}\text{Tc}(\text{DMPE})_2\text{Br}_2)\text{Br}$ und $(^{99m}\text{Tc}(\text{DMPE})_2\text{Cl}_2)\text{Cl}$, gewählt wird.
14. Komplex nach Anspruch 1, welcher $(^{99m}\text{Tc}(\text{Tetraphos})\text{Br}_2)\text{Br}$ ist.
15. Komplex nach einem der Ansprüche 12 bis 14, welcher in der trans-Konfiguration ist.
16. Komplex nach Anspruch 1 in Kombination mit einem pharmakologisch inerten Vehikel.
17. Komplex nach Anspruch 16, worin das Vehikel 50:50 Ethanol/Salzlösung ist.
18. Verfahren zur Herstellung eines kationischen, lipophilen Komplexes von ^{99m}Tc der Formel



worin

L ein neutraler, lipophiler Ligand ist, welcher mit einem ^{99m}Tc -Kation stark cheliert und welcher in der Lage ist, Tc^{+7} auf einen niedrigeren Wertigkeitszustand zu reduzieren;

X gleiche oder verschiedene einwertige, anionische Liganden sind, welches umfaßt:

Reduktion eines $^{99m}\text{Tc}^{+7}$ -Spezies zu einem Spezies mit niedrigerem Wertigkeitszustand mit einem Liganden L, worin $^{99m}\text{Tc}^{+7}$ in einer wäßrigen Phase vorliegt, worin der Ligand L in einer wasserunmischbaren Phase in sehr gutem Kontakt mit der wäßrigen Phase vorliegt und worin während der Reduktion das Spezies von ^{99m}Tc mit niedrigerem Wertigkeitszustand in die nichtwäßrige Phase überführt wird.

19. Verfahren nach Anspruch 18, worin nach der Überführung des Spezies von ^{99m}Tc mit niedrigerem Wertigkeitszustand in die wasserunmischbare Phase das Verfahren weiterhin umfaßt:

Absorbieren des Spezies in Komplexbildung mit dem Liganden L auf einem Material mit Adsorptionskapazität für Kationen, welches in der Lage ist, kationische Komplexe von neutralen oder anionischen Molekülen zu trennen und Eluieren des weitgehend reinen $(^{99m}\text{TcL}_2\text{X}_2)^+$ -Spezies daraus.

20. Ausrüstung, umfassend einen Träger, welcher aufgeteilt ist, um eine Reihe von Behältern in enger Begrenzung aufzunehmen, welche umfaßt:

- einen ersten Behälter, enthaltend eine ^{99m}Tc -Quelle;
- einen zweiten Behälter, enthaltend einen mehrwertigen, neutralen, lipophilen Liganden L, welcher mit einem ^{99m}Tc -Kation stark cheliert und in der Lage ist, mit diesem ^{99m}Tc -Kation einen kationischen, lipophilen Komplex mit einem n-Octanol/Salzlösung-Verteilungskoeffizienten größer als etwa 0,05 zu bilden; und
- einen dritten Behälter, enthaltend chromatographisches Material mit Adsorptionskapazität für Kationen.

21. Ausrüstung nach Anspruch 20, worin der zweite Behälter weiterhin ein Reduktionsmittel, welches in der Lage ist, ^{99m}Tc aus einem Wertigkeitszustand von +VII auf einen niedrigeren Wertigkeitszustand zu reduzieren, enthält.

22. Ausrüstung nach Anspruch 20, worin der dritte Behälter die Form einer kurzen Chromatographieöhre besitzt.

23. Ausrüstung nach Anspruch 20, worin der dritte Behälter die Form eines Spritzenadapters besitzt, welcher in der Lage ist, das chromatographische Material zwischen dem Zylinder der Spritze und der Nadel der Spritze zu halten.

24. Ausrüstung nach Anspruch 23, worin die Ausrüstung ebenfalls eine Spritze, welche sich dem Adapter anpassen kann, umfaßt.

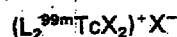
25. Ausrüstung nach Anspruch 20, worin das chromatographische Material aus der Gruppe, bestehend aus Aluminiumoxid, Siliciumoxid und einem Kationenaustauscherharz, gewählt wird.

26. Ausrüstung nach Anspruch 20, worin der ^{99m}Tc -Generator ein Mo-99 Molybdän-Generator ist.

27. Diagnostisches Produkt zur Abbildung der Leber, der Galle, des Herzmuskels, der Bauchspeicheldrüse und des Gehirns in einem Säuger, welches eine Abbildungsmenge eines kationischen, lipophilen Komplexes von Tc-99m nach einem der Ansprüche 1 bis 17 umfaßt.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines kationischen, lipophilen Komplexes von ^{99m}Tc der Formel:

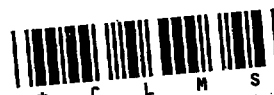


worin

L ein neutraler, mehrwertiger, lipophiler Ligand ist, welcher mit einem ^{99m}Tc -Kation stark cheliert, und welcher in der Lage ist, Tc^{+7} auf einen niedrigeren Wertigkeitszustand zu reduzieren;

X gleiche oder verschiedene einwertige, anionische Liganden sind oder in der Formel $(\text{L}_2^{99m}\text{TcX}_2)^+$ beide X Teil des gleichen zweizähligen Liganden sind, welcher in der Lage ist, die cis-Position eines ^{99m}Tc -Kations zu koordinieren, welches umfaßt:

Reduktion eines $^{99m}\text{Tc}^{+7}$ -Spezies zu einem Spezies mit niedrigerem Wertigkeitszustand mit einem Liganden L, worin $^{99m}\text{Tc}^{+7}$ in einer wäßrigen Phase vorliegt, worin der Ligand L in einer wasserunmisch-



baren Phase in sehr gutem Kontakt mit der wäßrigen Phase vorliegt und worin während der Reduktion das Spezies von ^{99m}Tc mit niedrigerem Wertigkeitszustand in die nichtwäßrige Phase überführt wird.

2. Verfahren nach Anspruch 1, worin nach der Überführung des Spezies von ^{99m}Tc mit niedrigerem Wertigkeitszustand in die wasserunmischbare Phase das Verfahren weiterhin umfaßt:

5 Absorbieren des Spezies in Komplexbildung mit dem Liganden L auf einem Material mit Adsorptionskapazität für Kationen, welches in der Lage ist, kationische Komplexe von neutralen oder anionischen Molekülen zu trennen und Eluieren des weitgehend reinen $(^{99m}\text{TcL}_2\text{X}_2)^+$ -Spezies daraus.

3. Verfahren nach Anspruch 1 oder 2 worin der kationische, lipophile Komplex von Tc-99m einen n-Octanol/Salzlösung-Verteilungskoeffizienten größer als etwa 0,05 besitzt.

10 4. Verfahren nach Anspruch 1 oder 2, worin der kationische, lipophile Komplex von ^{99m}Tc in unpolaren, wasserunmischbaren Lösungsmitteln löslich ist.

5. Verfahren nach Anspruch 4, worin der kationische, lipophile Komplex von ^{99m}Tc ebenfalls in polaren, wassermischbaren Lösungsmitteln löslich ist.

6. Verfahren nach Anspruch 1, worin L die Formel

15



besitzt, worin

n = 2 bis 5;

worin

20

A gewählt wird aus der Gruppe, bestehend aus einem substituierten oder unsubstituierten Alkylenradikal, einem homomonocyclischen oder homopolycyclischen, lipophilen, organischen Radikal und einem heteromonocyclischen oder heteropolycyclischen, organischen Radikal, enthaltend in wenigstens einem der Ringe ein Atom, gewählt aus der Gruppe, bestehend aus N, O, P, S oder B;

Y gleiche oder verschiedene neutrale, funktionelle Gruppen mit einem freien Elektronenpaar sind,

25

welches in der Lage ist, mit einem ^{99m}Tc -Kation einen Komplex zu bilden.

7. Verfahren nach Anspruch 6, worin n = 2 oder 3.

8. Verfahren nach Anspruch 6, worin A $-\text{CH}_2\text{CH}_2-$ ist.

9. Verfahren nach Anspruch 6, worin Y gleiche oder verschiedene funktionelle Gruppen, gewählt aus der Gruppe, bestehend aus Y^1R_2 und Y^2R , sind, worin

30

Y^1 ein Atom, gewählt aus der Gruppe, bestehend aus N, P, As, Sb und Bi, ist,

Y^2 ein Atom, gewählt aus der Gruppe, bestehend aus O, S, Se und Te, ist und

R aus der Gruppe, bestehend aus Wasserstoff, einer unsubstituierten, geradkettigen oder verzweigt-kettigen C_1-C_{15} Alkylgruppe und einer geradkettigen oder verzweigt-kettigen C_1-C_{15} Alkylgruppe, substituiert entlang oder an der Kohlenwasserstoffkette mit Sauerstoff, Stickstoff, Schwefel oder Phosphor,

35

gewählt wird.

10. Verfahren nach Anspruch 6, worin die Liganden X gleiche oder verschiedene Liganden, gewählt aus der Gruppe, bestehend aus F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- und RS^- , sind, worin

R aus der Gruppe, bestehend aus einer unsubstituierten, geradkettigen oder verzweigt-kettigen C_1-C_{15} Alkylgruppe und einer geradkettigen oder verzweigt-kettigen C_1-C_{15} Alkylgruppe, substituiert entlang oder

40

an der Kohlenwasserstoffkette mit Sauerstoff, Stickstoff, Schwefel oder Phosphor, gewählt wird.

11. Verfahren nach Anspruch 4, worin L gewählt wird aus der Gruppe, bestehend aus

DMPE $(\text{CH}_3)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{CH}_3)_2$;

Diars $(\text{o}-\text{C}_6\text{H}_4(\text{As}(\text{CH}_3)_2))_2$;

Diphos $(\text{C}_6\text{H}_5)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{C}_6\text{H}_5)_2$;

45

Tris(1-pyrazolyl)borat;

Porphyrin;

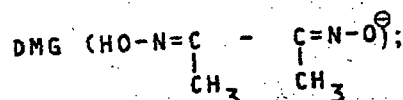
Tetraphos $\text{P}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_3$;

DAE $(\text{C}_6\text{H}_5)_2\text{As}-\text{CH}_2\text{CH}_2\text{As}(\text{C}_6\text{H}_5)_2$;

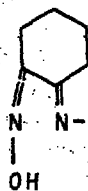
DIEN $(\text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2)$;

50

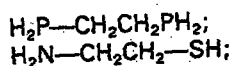
PPN $(\text{RN}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_2)$, worin R = H oder ein substituiertes oder unsubstituiertes C_1-C_{15} Alkyl;



55



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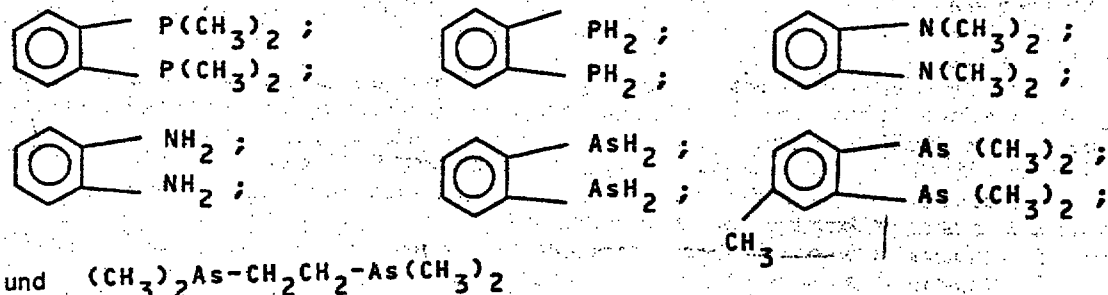


$H_2As-CH_2CH_2-AsH_2$;
 $H_2N-CH_2CH_2-NH_2$;
 $HS-CH_2CH_2-SH$;
 $(CH_3)_2N-CH_2CH_2-N(CH_3)_2$;
 Tris(1-pyrazolyl)methan;

5

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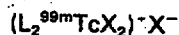
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12. Verfahren nach Anspruch 11, worin L aus der Gruppe, bestehend aus Diars, DMPE und Tetraphos, gewählt wird.
13. Verfahren nach Anspruch 1, worin der kationische, lipophile Komplex von ^{99m}Tc ($^{99m}Tc(Diars)_2Br_2$)Br oder ($^{99m}Tc(Diars)_2Cl_2$)Cl ist.
14. Verfahren nach Anspruch 1, worin der kationische, lipophile Komplex von ^{99m}Tc ($^{99m}Tc(DMPE)_2Br_2$)Br oder ($^{99m}Tc(DMPE)_2Cl_2$)Cl ist.
15. Verfahren nach Anspruch 1, worin der kationische, lipophile Komplex von ^{99m}Tc ($^{99m}Tc(Tetraphos)_2Br_2$)Br ist.
16. Verfahren nach einem der Ansprüche 12 bis 15, worin der kationische, lipophile Komplex von ^{99m}Tc in der trans-Konfiguration vorliegt.
17. Ausrüstung, umfassend einen Träger, welcher aufgeteilt ist, um eine Reihe von Behältern in enger Begrenzung aufzunehmen, welche umfaßt:
 - einen ersten Behälter, enthaltend eine ^{99m}Tc -Quelle;
 - einen zweiten Behälter, enthaltend einen mehrwertigen, neutralen, lipophilen Liganden L, welcher mit einem ^{99m}Tc -Kation stark cheliert und in der Lage ist, mit diesem ^{99m}Tc -Kation einen kationischen, lipophilen Komplex mit einem n-Octanol/Salzlösung-Verteilungskoeffizienten größer als etwa 0,05 zu bilden; und
 - einen dritten Behälter, enthaltend chromatographisches Material mit Adsorptionskapazität für Kationen.
18. Ausrüstung nach Anspruch 17, worin der zweite Behälter weiterhin ein Reduktionsmittel, welches in der Lage ist, ^{99m}Tc aus einem Wertigkeitszustand von +VII auf einen niedrigeren Wertigkeitszustand zu reduzieren, enthält.
19. Ausrüstung nach Anspruch 17, worin der dritte Behälter die Form einer kurzen Chromatographieröhre besitzt.
20. Ausrüstung nach Anspruch 17, worin der dritte Behälter die Form eines Spritzenadapters besitzt, welcher in der Lage ist, das chromatographische Material zwischen dem Zylinder der Spritze und der Nadel der Spritze zu halten.
21. Ausrüstung nach Anspruch 20, worin die Ausrüstung ebenfalls eine Spritze, welche sich dem Adapter anpassen kann, umfaßt.
22. Ausrüstung nach Anspruch 17, worin das chromatographische Material aus der Gruppe, bestehend aus Aluminiumoxid, Siliciumoxid und einem Kationenaustauscherharz, gewählt wird.
23. Ausrüstung nach Anspruch 17, worin der ^{99m}Tc -Generator ein Mo-99 Molybdän-Generator ist.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI NL SE

1. Complexe lipophile cationique du Tc-99m ayant un coefficient de partage n-octanol/sérum physiologique supérieur à environ 0,05.
2. Complexe de la revendication 1, qui est soluble dans des solvants non polaires non-miscibles à l'eau.
3. Complexe de la revendication 2, qui est également soluble dans des solvants polaires miscibles à l'eau.
4. Complexe de la revendication 1, qui répond à la formule

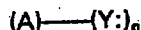


dans laquelle L est un ligand lipophile neutre polyvalent qui est fortement chélatant vis-à-vis d'un cation ^{99m}Tc ; X sont des ligands anioniques monovalents identiques ou différents; où, dans la formule



($L_2^{99mTc}X_2$)⁺, les deux X font partie du même ligand bicoordonné capable de coordonner les positions *cis* d'un cation ^{99m}Tc .

5. Complexe de la revendication 4, dans lequel L répond à la formule



dans laquelle

$n = 2-5$;

dans laquelle

A est choisi dans le groupe constitué d'un radical alkylène substitué ou non substitué, d'un radical organique lipophile homocyclique ou homopolycyclique, et d'un radical organique hétéromonocyclique ou hétéropolycyclique contenant dans au moins un de ses cycles un atome choisi dans le groupe constitué de N, O, P, S ou B;

Y sont des groupes fonctionnels neutres identiques ou différents ayant une paire d'électrons libres capable de se complexer avec un cation ^{99m}Tc .

6. Complexe de la revendication 5, dans lequel $n = 2$ ou 3.

7. Complexe de la revendication 5, dans lequel A est $-CH_2CH_2-$.

8. Complexe de la revendication 5, dans lequel Y: sont des groupes fonctionnels identiques ou différents choisis dans le groupe constitué de Y^1R_2 et de Y^2R , où

Y^1 est un atome choisi dans le groupe constitué de N, P, As, Sb, et Bi;

Y^2 est un atome choisi dans le groupe constitué de O, S, Se, et Te et

R est choisi dans le groupe constitué de l'hydrogène, d'un groupe alkyle non substitué à chaîne linéaire ou ramifiée en C_1-C_{15} , et d'un groupe alkyle à chaîne linéaire ou ramifiée en C_1-C_{15} substitué le long ou sur la chaîne hydrocarbonée avec de l'oxygène, de l'azote, du soufre ou du phosphore.

9. Complexe de la revendication 5, dans lequel les ligands X sont des ligands identiques ou différents choisis dans le groupe constitué de F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- , et RS^- , dans lequel R est choisi dans le groupe constitué d'un groupe alkyle non substitué linéaire ou ramifié en C_1-C_{15} et d'un groupe alkyle linéaire ou ramifié en C_1-C_{15} substitué le long ou sur la chaîne hydrocarbonée avec de l'oxygène, de l'azote, du soufre ou du phosphore.

10. Complexe de la revendication 4, dans lequel L est choisi dans le groupe constitué de:

DMPE ((CH_3)₂P- CH_2CH_2 -P(CH_3)₂);

diars ($o-C_6H_4(As(CH_3)_2)$);

diphos ((C_6H_5)₂P- CH_2CH_2 -P(C_6H_5)₂);

le borate de tris (1-pyrazolyle);

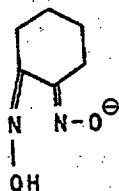
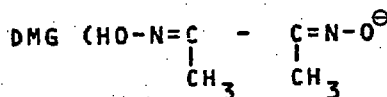
la porphyrine;

tétraphos (P($CH_2CH_2P(C_6H_5)_2$)₃);

DAE ((C_6H_5)₂As- CH_2CH_2 As(C_6H_5)₂);

DIEN ($H_2N-CH_2CH_2NHCH_2CH_2NH_2$);

PPN (RN($CH_2CH_2P(C_6H_5)_2$)₂, où R = H ou un alkyle en C_1-C_{15} substitué ou non;



$H_2P-CH_2CH_2PH_2$;

$H_2N-CH_2CH_2-SH$;

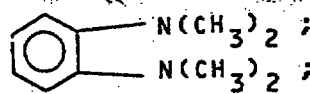
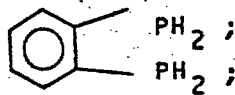
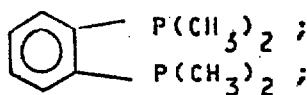
$H_2As-CH_2CH_2-AsH_2$;

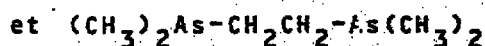
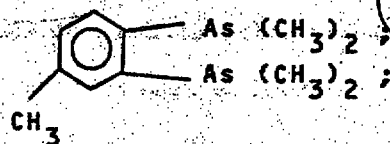
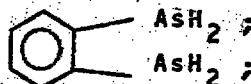
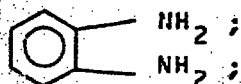
$H_2N-CH_2CH_2-NH_2$;

$HS-CH_2CH_2-SH$;

(CH_3)₂N- CH_2CH_2 -N(CH_3)₂;

tris (1-pyrazolyl) méthane;





- 10 11. Complexe de la revendication 10, dans lequel L est choisi dans le groupe constitué du diars, du DMPE et du tetraphos.
12. Complexe de la revendication 1, qui est choisi dans le groupe constitué du $(^{99\text{m}}\text{Tc}(\text{diars})_2\text{Br}_2)\text{Br}$ et du $(^{99\text{m}}\text{Tc}(\text{diars})_2\text{Cl}_2)\text{Cl}$.
13. Complexe de la revendication 1, qui est choisi dans le groupe constitué du $(^{99\text{m}}\text{Tc}(\text{DMPE})_2\text{Br}_2)\text{Br}$ et du $(^{99\text{m}}\text{Tc}(\text{DMPE})_2\text{Cl}_2)\text{Cl}$.
14. Complexe de la revendication 1, qui est $(^{99\text{m}}\text{Tc}(\text{tétrapos})\text{Br}_2)\text{Br}$.
15. Complexe suivant l'une quelconque des revendications 12—14, qui est dans la configuration trans.
16. Complexe suivant la revendication 1, associé à un excipient pharmacologiquement inerte.
17. Complexe de la revendication 16, dans lequel cet excipient est de l'éthanol/sérum physiologique 50:50.
18. Procédé de préparation d'un complexe lipophile cationique du $^{99\text{m}}\text{Tc}$ répondant à la formule:



25 dans laquelle L est un ligand lipophile neutre qui est fortement chélatant vis-à-vis d'un cation $^{99\text{m}}\text{Tc}$, et qui est capable de réduire Tc^{-7} à un état de valence inférieur; X sont des ligands anioniques monovalents identiques ou différents, qui comprend la réduction d'une espèce $^{99\text{m}}\text{Tc}^{+7}$ en une espèce dans un état de valence inférieure avec un ligand L, dans lequel le $^{99\text{m}}\text{Tc}^{+7}$ est présent dans une phase aqueuse, dans lequel le ligand L est présent dans une phase non-miscible à l'eau en contact intime avec cette phase aqueuse, et dans lequel au cours de la réduction, cette espèce dans un état de valence inférieur du $^{99\text{m}}\text{Tc}$ est transférée dans cette phase non-aqueuse.

19. Procédé suivant la revendication 18, dans lequel, après ce transfert de l'espèce du $^{99\text{m}}\text{Tc}$ dans un état de valence inférieur dans cette phase non-miscible à l'eau, le procédé comprend en outre: l'absorption de cette espèce en complexation avec ce ligand L, sur une matière ayant une capacité d'absorption pour les cations, capable de séparer les complexes cationiques des molécules neutres ou anioniques et l'élution d'une espèce $(^{99\text{m}}\text{TcL}_2\text{X}_2)^+$ pratiquement pure de celle-ci.

20. Trousse comprenant un support compartimenté pour recevoir une série de récipients étroitement serrés les uns contre les autres, qui comprend:

- un premier récipient contenant une source de $^{99\text{m}}\text{Tc}$;
- 40 un second récipient contenant un ligand lipophile neutre polyvalent L qui est fortement chélatant vis-à-vis d'un cation $^{99\text{m}}\text{Tc}$ et est capable de former avec ce cation $^{99\text{m}}\text{Tc}$ un complexe cationique lipophile ayant un coefficient de partage n-octanol/sérum physiologique supérieur à environ 0,05; et
- un troisième récipient contenant une matière chromatographique ayant une capacité d'adsorption pour les cations.

21. Trousse de la revendication 20, dans laquelle ce second récipient contient en outre un agent réducteur capable de réduire le $^{99\text{m}}\text{Tc}$ d'un état de valence +VII à un état de valence inférieur.

22. Trousse de la revendication 20, dans laquelle ce troisième récipient est sous la forme d'un tube chromatographique court.

23. Trousse de la revendication 20, dans laquelle ce troisième récipient est sous la forme d'un adaptateur de seringue capable de maintenir une matière chromatographique entre le corps de cette seringue et l'aiguille de cette seringue.

24. Trousse de la revendication 23, dans laquelle cette trousse contient aussi une seringue capable de s'adapter à cet adaptateur.

25. Trousse de la revendication 20, dans laquelle cette matière chromatographique est choisie dans le groupe constitué de l'alumine, de la silice et d'une résine échangeuse cationique.

26. Trousse de la revendication 20, dans laquelle le générateur de $^{99\text{m}}\text{Tc}$ est un générateur de molybdène Mo-99.

27. Produit diagnostique pour la visualisation hépatobiliaire, myocardique, pancréatique et cérébrale chez un mammifère comprenant, une quantité visualisante d'un complexe lipophile cationique de $\text{Tc-}^{99\text{m}}$ suivant l'une quelconque des revendications 1 à 17.





Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un complexe lipophile cationique de ^{99m}Tc répondant à la formule:



dans laquelle L est un ligand lipophile polyvalent neutre qui est fortement chélatant vis-à-vis d'un cation ^{99m}Tc , et qui est capable de réduire Tc^{+7} à un état de valence inférieur; X sont des ligands anioniques monovalents identiques ou différents; où, dans la formule $(\text{L}_2^{99m}\text{TcX}_2)^+$, les deux X font partie du même ligand bicoordonné capable de coordonner les positions *cis* d'un cation ^{99m}Tc , qui comprend:
la réduction d'une espèce $^{99m}\text{Tc}^{+7}$ dans un état de valence inférieur avec un ligand L, dans lequel le $^{99m}\text{Tc}^{+7}$ est présent dans une phase aqueuse, dans lequel le ligand L est présent dans une phase non-miscible à l'eau en contact intime avec cette phase aqueuse, et dans lequel au cours de la réduction, cette espèce dans un état de valence inférieur du ^{99m}Tc est transférée dans cette phase non-aqueuse.

2. Procédé de la revendication 1, dans lequel, après ce transfert de l'espèce du ^{99m}Tc dans un état de valence inférieur dans cette phase non-miscible à l'eau, le procédé comprend en outre:
l'absorption de cette espèce en complexation avec ce ligand L, sur une matière ayant une capacité d'adsorption pour les cations, capable de séparer les complexes cationiques de molécules neutres ou anioniques et l'élution d'une espèce $(^{99m}\text{TcL}_2\text{X}_2)^+$ pratiquement pure de celle-ci.

3. Procédé des revendications 1 ou 2, dans lequel le complexe lipophile cationique du TC-99m a un coefficient de partage n-octanol/sérum physiologique supérieur à environ, 0,05.

4. Procédé suivant les revendications 1 ou 2, dans lequel le complexe lipophile cationique de ^{99m}Tc est soluble dans des solvants non polaires non miscibles à l'eau.

5. Procédé de la revendication 4, dans lequel le complexe lipophile cationique de ^{99m}Tc est également soluble dans des solvants polaires miscibles à l'eau.

6. Procédé de la revendication 1, dans lequel L répond à la formule:



dans laquelle

n = 2-5;

dans laquelle

A est choisi dans le groupe constitué d'un radical alkylène substitué ou non substitué, d'un radical organique lipophile homomonocyclique ou homopolycyclique, et d'un radical organique hétéromonocyclique ou hétéropolycyclique contenant, dans au moins un de ses cycles un atome choisi dans le groupe constitué de N, O, P, S ou B;

Y sont des groupes fonctionnels neutres identiques ou différents ayant une paire d'électrons libres capable de se complexer avec un cation ^{99m}Tc .

7. Procédé de la revendication 6, dans lequel n = 2 ou 3.

8. Procédé de la revendication 6, dans lequel A est $-\text{CH}_2\text{CH}_2-$.

9. Procédé de la revendication 6, dans lequel Y: sont des groupes fonctionnels identiques ou différents choisis dans le groupe constitué de Y^1R_2 et de Y^2R , où

Y^1 est un atome choisi dans le groupe constitué de N, P, As, Sb, et Bi;

Y^2 est un atome choisi dans le groupe constitué de O, S, Se, et Te et

R est choisi dans le groupe constitué de l'hydrogène, d'un groupe alkyle non substitué à chaîne linéaire ou ramifiée en C_1-C_{15} , et d'un groupe alkyle à chaîne linéaire ou ramifiée en C_1-C_{15} substitué le long ou sur la chaîne hydrocarbonée avec de l'oxygène, de l'azote, du soufre ou du phosphore.

10. Procédé de la revendication 6, dans lequel ces ligands X sont des ligands identiques ou différents choisis dans le groupe constitué de F^- , Cl^- , Br^- , I^- , SCN^- , N_3^- , CN^- , et RS^- , dans lequel R est choisi dans le groupe constitué d'un groupe alkyle non substitué linéaire ou ramifié en C_1-C_{15} , et d'un groupe alkyle à chaîne linéaire ou ramifié, substitué le long ou sur la chaîne hydrocarbonée avec de l'oxygène, de l'azote, du soufre ou du phosphore.

11. Procédé de la revendication 4, dans lequel L est choisi dans le groupe constitué de:

DMPE $((\text{CH}_3)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{CH}_3)_2)$;

diars $(\text{o}-\text{C}_6\text{H}_4(\text{As}(\text{CH}_3)_2)_2)$;

diphos $((\text{C}_6\text{H}_5)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{C}_6\text{H}_5)_2)$;

le borate de tris (1-pyrazolyle) la porphyrine;

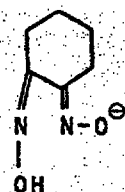
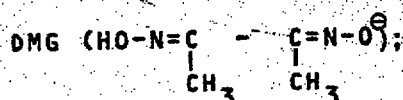
tétraphos $(\text{P}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_3)$;

DAE $((\text{C}_6\text{H}_5)_2\text{As}-\text{CH}_2\text{CH}_2\text{A}(\text{C}_6\text{H}_5)_2)$;

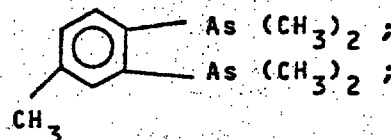
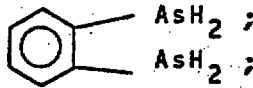
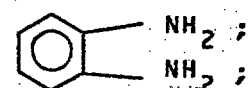
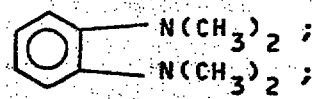
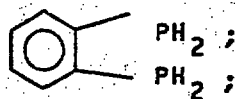
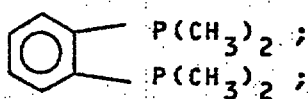
DIEN $(\text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2)$;

PPN $(\text{RN}(\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_2)_2)$, où R = H ou un alkyle en C_1-C_{15} substitué ou non;





$\text{H}_2\text{P}-\text{CH}_2\text{CH}_2\text{PH}_2;$
 $\text{H}_2\text{N}-\text{CH}_2\text{CH}_2-\text{SH};$
 $\text{H}_2\text{As}-\text{CH}_2\text{CH}_2-\text{AsH}_2;$
 $\text{H}_2\text{N}-\text{CH}_2\text{CH}_2-\text{NH}_2;$
 $\text{HS}-\text{CH}_2\text{CH}_2-\text{SH};$
 $(\text{CH}_3)_2\text{N}-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2;$
 tris (1-pyrazolyl) méthane;



et $(\text{CH}_3)_2\text{As}-\text{CH}_2\text{CH}_2-\text{As}(\text{CH}_3)_2$

12. Procédé de la revendication 11, dans lequel L est choisi dans le groupe constitué du diars, du DMPE et du tétraphos.

13. Procédé de la revendication 1, dans lequel le complexe lipophile cationique de $^{99\text{m}}\text{Tc}$ est le $(^{99\text{m}}\text{Tc}(\text{diars})_2\text{Br}_2)\text{Br}$ ou le $(^{99\text{m}}\text{Tc}(\text{diars})_2\text{Cl}_2)\text{Cl}$.

14. Procédé de la revendication 1, dans lequel le complexe lipophile cationique de $^{99\text{m}}\text{Tc}$ est le $(^{99\text{m}}\text{Tc}(\text{DMPE})_2\text{Br}_2)\text{Br}$ ou le $(^{99\text{m}}\text{Tc}(\text{DMPE})_2\text{Cl}_2)\text{Cl}$.

15. Procédé de la revendication 1, dans lequel le complexe lipophile cationique de $^{99\text{m}}\text{Tc}$ est le $(^{99\text{m}}\text{Tc}(\text{tétraphos})\text{Br}_2)\text{Br}$.

16. Procédé de l'une quelconque des revendications 12—15, dans lequel le complexe lipophile cationique du $^{99\text{m}}\text{Tc}$ est dans la configuration trans.

17. Trousse comprenant un support compartimenté pour recevoir une série de récipients étroitement serrés les uns contre les autres, qui comprend:

un premier récipient contenant une source de $^{99\text{m}}\text{Tc}$;

un second récipient contenant un ligand lipophile neutre polyvalent L qui est fortement chélatant vis-à-vis d'un cation $^{99\text{m}}\text{Tc}$ et est capable de former avec ce cation $^{99\text{m}}\text{Tc}$ un complexe cationique lipophile ayant un coefficient de partage n-octanol/sérum physiologique supérieur à environ 0,05; et

un troisième récipient contenant une matière chromatographique ayant une capacité d'adsorption pour les cations.

18. Trousse de la revendication 17, dans laquelle ce second récipient contient en outre un agent réducteur capable de réduire le $^{99\text{m}}\text{Tc}$ d'un état de valence +VII à un état de valence inférieur.

19. Trousse de la revendication 17, dans laquelle ce troisième récipient est sous la forme d'un tube chromatographique court.

20. Trousse de la revendication 17, dans laquelle ce troisième récipient est sous la forme d'un adaptateur de seringue capable de maintenir une matière chromatographique entre le corps de cette seringue et l'aiguille de cette seringue.

21. Trousse de la revendication 17, dans laquelle cette trousse contient aussi une seringue capable de s'adapter à cet adaptateur.

22. Trousse de la revendication 17, dans laquelle cette matière chromatographique est choisie dans le groupe constitué de l'alumine, de la silice et d'une résine échangeuse cationique.

23. Trousse de la revendication 17, dans laquelle le générateur de $^{99\text{m}}\text{Tc}$ est un générateur de molybdène Mo-99.

