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(71) Applicant: MALLINCKRODT MEDICAL, INC. [US/US]; 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

(72) Inventors: NEUMANN, William, L.; 434 W. Madison, Kirkwood, MO 63122 (US). RAJAGOPALAN, Raghavan; 13031 Vinson Court, Maryland Heights, MO 63043 (US).

(74) Agents: STIERWALT, Brian, K. et al.; Mallinckrodt Medical, Inc., 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

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(54) Title: HEXADENTATE LIGANDS USEFUL IN RADIOGRAPHIC IMAGING AGENTS

(57) Abstract

The present invention relates particularly to novel preorganized hexadentate ligands that are suitable for complexing with a radionuclide, and are useful as general imaging agents for diagnostic purposes.

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HEXADENTATE LIGANDS USEFUL IN RADIOGRAPHIC IMAGING AGENTS

This is a continuation-in-part application of United States application serial number 07/627,176 filed December 14, 1990.

Background of the Invention

The present invention relates to novel ligands for forming radionuclide complexes, new complexes incorporating such ligands, processes for preparing such complexes, imaging agents incorporating such complexes, and methods of imaging using such imaging agents.

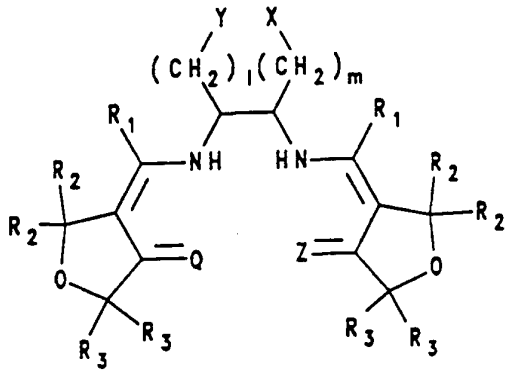
The use of radiographic imaging agents for visualizing skeletal structures, organs, or tissues, is well known in the area of biological and medical research and diagnostic procedures. The procedure whereby such imaging is accomplished, generally involves the preparation of radioactive agents, which, when introduced to the biological subject, are localized in the specific skeletal structures, organs or tissues to be studied. The localized radioactive agents may then be traced, plotted or scintiphotographed by radiation detectors, such as, traversing scanners or scintillation cameras. The distribution and relative intensity of the detected radioactive agents indicates the position of the tissue in which the agent is localized, and also shows the presence of aberrations, pathological conditions or the like.

In general, the radiographic imaging agents comprise radionuclide-labelled compounds; such as complexes of technetium 99m, rhenium 186 or rhenium 188, or other applicable radionuclides; with appropriate carriers, and auxiliary agents, such as delivery vehicles suitable for

injection into, or aspiration by, the patient, physiological buffers and salts, and the like.

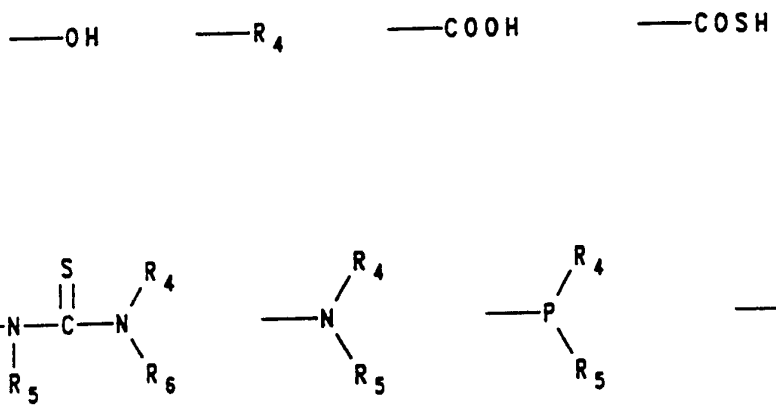
Detailed Description of the Invention

The present invention relates particularly to novel preorganized hexadentate ligands that are suitable for complexing with a radionuclide, and are useful as general imaging agents for diagnostic purposes. In particular the present invention relates to novel ligands having the general formula:



Formula I

wherein R_1, R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl and carbamoyl; l and m may be the same or different and are from 1 to 6; Q and Z may be the same or different and are an O, N or S atom; X and Y may be the same or different and are selected from the group consisting of



wherein R_4, R_5 and R_6 may be the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl, amino, alkylamino, aminoalkyl, and carbamoyl.

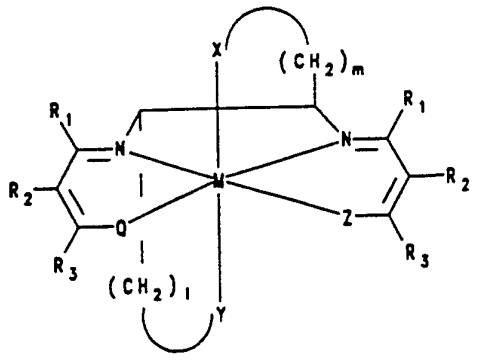
In a preferred embodiment, ligands according to the present invention have the general formula I above, wherein R_1 is hydrogen; R_2 and R_3 are methyl groups; l and m are 3; Q and Z are oxygen atoms; and X and Y are the same and are as defined above. In a further preferred embodiment, X and Y are the same and are

The novel ligands described above, may be incorporated into radionuclide complexes used as radiographic imaging agents. The complexes of the present invention are prepared by reacting one of the aforementioned ligands with a radionuclide containing solution under radionuclide complex forming reaction

conditions. In particular, if a technetium agent is desired, the reaction is carried out with a pertechnetate solution under technetium 99m complex forming reaction conditions. The solvent may then be removed by any appropriate means, such as evaporation. The complexes are then prepared for administration to the patient by dissolution or suspension in a pharmaceutically acceptable vehicle.

The ligands of the present invention may be prepared from commercially available starting materials such as 2-nitrobenzylbromide, hydroxyethylethylenediamine, etc. by standard synthetic methods as described in the following Examples.

Radionuclide complexes according to the present invention may have the general formula:



Formula II

wherein M is an appropriate radionuclide such as technetium or rhenium, and wherein R_1, R_2, R_3, l, m, X, Y, Q, and Z are as defined above in formula I. In a preferred embodiment a technetium radionuclide complex

having the general formula II may be formed from a pertechnetate solution and a ligand having the general formula I above, wherein R_1 is a methyl group, R_2 is hydrogen, R_3 is a methyl group, l = 3, m = 3, Q = O, Z = O, and wherein X and Y are the same and are as defined above.

The radionuclide containing solution may be obtained from radionuclide generators in a known manner. For example, when forming a technetium complex, the pertechnetate solution may be obtained from a technetium generator in a known manner. The radionuclide complex forming reaction is then carried out under appropriate reaction conditions. For example, the technetium 99m complex forming reaction is carried out under technetium complex forming temperatures, e.g. 20° C to 100°C for 10 minutes to several hours. A large excess of the appropriate ligands over the radionuclide complex forming amounts is preferably used. For example, when forming a technetium complex, at least a ten fold excess of the ligands over the pertechnetate solution is used. The pertechnetate is used in technetium complex forming amounts, e.g. about 10^{6} to 10^{12} molar amounts.

The present invention also relates to imaging agents containing a radionuclide complex as described above, in an amount sufficient for imaging, together with a pharmaceutically acceptable radiological vehicle. The radiological vehicle should be suitable for injection or aspiration, such as human serum albumin; aqueous buffer solutions, e.g tris(hydromethyl) aminomethane (and its salts), phosphate, citrate, bicarbonate, etc; sterile water; physiological saline; and balanced ionic solutions containing chloride and or dicarbonate salts or normal blood plasma cations such as Ca^{+2}, Na^{+}, K^{+}, and Mg^{+2}.

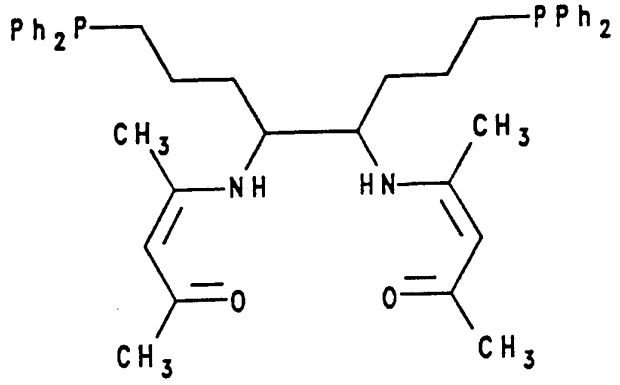
The concentration of the imaging agent according to the present invention in the radiological vehicle should be sufficient to provide satisfactory imaging, for example, when using an aqueous solution, the dosage is about 1.0 to 50 millicuries. The imaging agent should be administered so as to remain in the patient for about 1 to 3 hours, although both longer and shorter time periods are acceptable. Therefore, convenient ampules containing 1 to 10 ml of aqueous solution may be prepared.

Imaging may be carried out in the normal manner, for example by injecting a sufficient amount of the imaging composition to provide adequate imaging and then scanning with a suitable machine, such as a gamma camera.

The complexes according to the present invention may be prepared in accordance with the examples set forth below.

Example 1

Preparation of



Acetylacetone (1.51 g, 15.1 mmol) was added to a solution of 4,5-diamino-1,8-bis(dephenylphosphoro)-octane (3.40 g, 7.50 mmol) in methanol (20 ml) and the mixture was heated to reflux for 5 minutes, allowed to cool and stirred at ambient temperature for 1 hour. The solvent was removed under reduced pressure and the residue was triturated with hexanes (5 X 50 ml). The combined hexane extracts were evaporated to yield a viscous oil. This crude material was purified by radial chromatography (SiO_2, 3:1 hexanes - ethylacetate) to furnish the desired ligand as a yellow viscous oil.

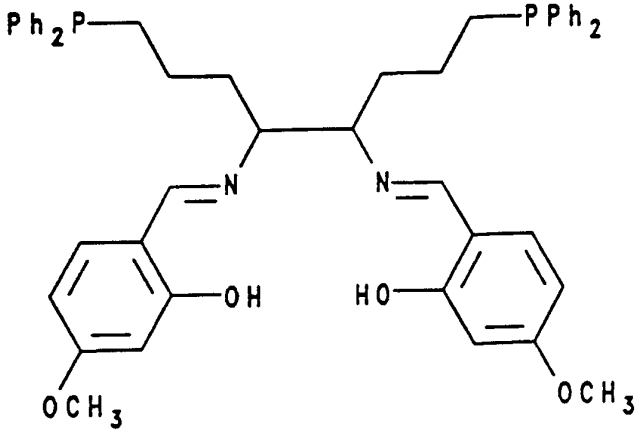
H-NMR (toluene-d_8): δ 11.22 (d,2H), 6.95 - 7.55 (m, 20H), 4.40 (S, 2H), 2,10 (m, 2H), 1.95 - 2.05 (multiple singlets, 12H), .95 - 2.05 (m, 12H).

^{13}C-NMR (toluene-d_8): δ 195.5 (S), 162.4 (S), 140.5 (S), 140.3 (S), 140.2 (S), 134.0 (d), 133.8 (d), 133.7 (d), 133.6 (d), 133.4 (d), 132.5 (d), 132.4 (d), 131.4 (d), 131.3 (d), 95.9 (d), 58.5 (d), 54.8 (d), 38.3 ($-CH_2-$, J_{PCCC} = 12.3 Hz), 35.0 ($-CH_2-$, J_{PCCC} = 12.3 Hz), 29.0 (q), 28.6 ($-CH_2-$, J_{PCC} = 12.6 Hz), 28.5 ($-CH_2-$, J_{PCC} = 7.5 Hz), 23.0 ($-CH_2-P-$, J_{PC} = 16.9 Hz), 19.2 (q).

^{31}P-NMR (toluene-d_8): δ -18.0.

Example 2

Preparation of

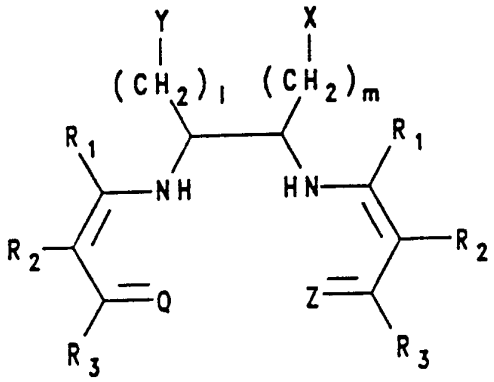


4-Methoxysalicylaldehyde (2.43 g, 16.0 mmol) was added to a solution of 4,5-diamino-1,8-bis (diphenylphosphine)octane (3.60 g, 7.99 mmol) in methanol (25 ml) and the resulting yellow mixture was heated to reflux for 5 minutes, allowed to cool and stirred for 1 hour at ambient temperature. The solvent was removed under reduced pressure and the yellow residue was triturated with hexanes (3 X 50 ml) to provide 5.77 g (93%) or the ligand as an amorphous yellow solid. ^{13}C-NMR (benzene-d_6): δ 165.6 (d), 165.5 (S), 164.6 (S), 140.3 (S), 140.2 (S), 140.0 (S), 135.7 (S), 135.0 (d), 134.8 (d), 134.0 (d), 133.9 (d), 133.8 (d), 133.7 (d), 133.6 (d), 133.4 (d), 131.6 (d), 131.5 (d), 113.2 (d), 107.4 (d), 101.8 (d), 73.3 (d), 55.1 (q), 34.3 (-CH_2-, J_{PCCC} = 12.2 Hz), 28.4 (-CH_2-, J_{PCC} = 12.7 Hz), 23.1 (-CH_2-P-, J_{PC} = 17.0 Hz). ^{31}P-NMR (benzene-d_6): δ -17.8.

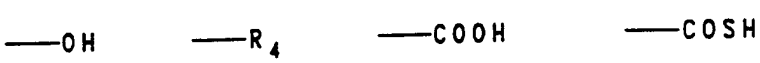
The foregoing has been a discussion of the preferred embodiments of the present invention, but is not intended to limit the invention in any way. Rather, many modifications, variations and changes in detail may be made within the scope of the present invention.

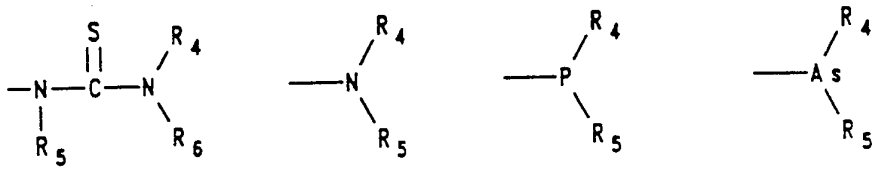
What is claimed is:

1. A ligand useful in forming radionuclide complexes, said ligand having the general formula:



wherein R_1, R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl and carbamoyl; l and m may be the same or different and are from 2 to 5; Q and Z may be the same or different and are an O, N or S atom; and X and Y may be the same or different and are selected from the group consisting of



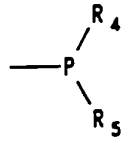


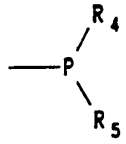
wherein R_4, R_5 and R_6 may be the same or different and are

selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl, amino, alkylamino, aminoalkyl, and carbamoyl.

2. A ligand accroding to claim 1, wherein either R_1 and R_2, or R_2 and R_3 together may form a carbocyclic or heterocyclic ring of 5 to 7 members.

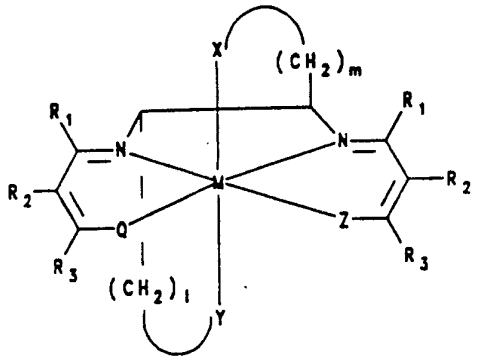
3. A ligand according to claim 1, wherein R_1 and R_3 are methyl groups; R_2 is hydrogen; l and m are 3; and Q and Z are oxygen atoms.

4. A ligand according to claim 1, wherein R_1 and R_3 are methyl groups; R_2 is hydrogen; l and m are 3; Q and Z are oxygen atoms; and X and Y are  wherein R_4 and R_5 are phenyl groups.

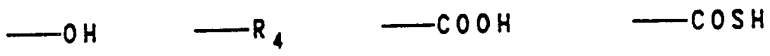
5. A ligand according to claim 1, wherein R_1 is hydrogen; R_2 and R_3 together form a carbocyclic ring; l and m are 3; Q and Z are oxygen atoms; and X and Y are  wherein R_4 and R_5 are phenyl groups.

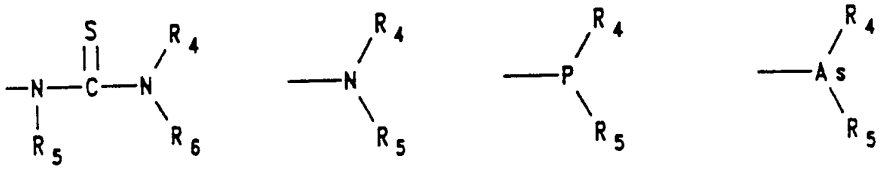
6. A ligand according to claim 5, wherein said carbocyclic ring is methoxybenzene.

7. A radionuclide complex having the general formula:



wherein M is a radionuclide; and wherein R_1, R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly-hydroxyalkyl, mono- or poly- alkoxyalkyl, alkoxycarbonyl and carbamoyl; l and m may be the same or different and are from 2 to 5; Q and Z may be the same or different and are an O, N or S atom; X and Y may be the same or different and are selected from the group consisting of



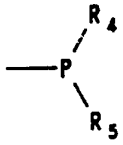


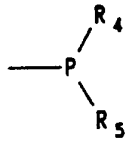
wherein R_4, R_5 and R_6 may be the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl, amino, alkylamino, aminoalkyl, and carbamoyl.

8. A complex according to claim 7, wherein either R_1 and R_2, or R_2 and R_3 together may form a carbocyclic or heterocyclic ring of 5 to 7 members.

9. A complex according to claim 7, wherein M is technetium or rhenium.

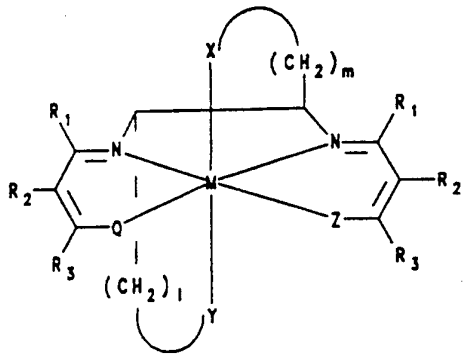
10. A complex according to claim 7, wherein R_1 is a methyl group, R_2 is hydrogen, R_3 is a methyl group, l = 3, m = 3, Q = O, Z = O, and wherein X and Y are the same.

11. A complex according to claim 7, wherein R_1 and R_3 are methyl groups; R_2 is hydrogen; l and m are 3; Q and Z are oxygen atoms; and X and Y are  wherein R_4 and R_5 are phenyl groups.

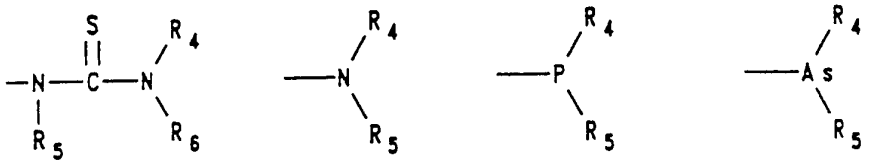
12. A complex according to claim 7, wherein R_1 is hydrogen; R_2 and R_3 together form a carbocyclic ring; l and m are 3; Q and Z are oxygen atoms; and X and Y are  wherein R_4 and R_5 are phenyl groups.

13. A complex according to claim 12, wherein said carbocyclic ring is methoxybenzene.

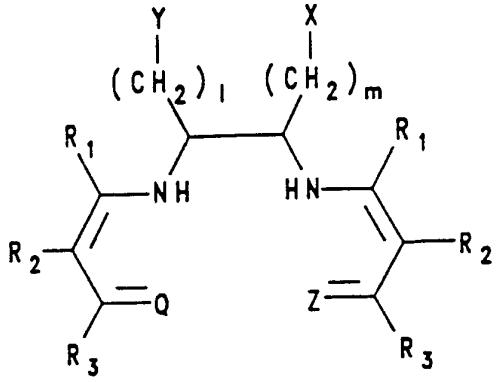
14. A method of making a radionuclide complex having the general formula:



wherein M is a radionuclide; and wherein R_1, R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly-hydroxyalkyl, mono- or poly- alkoxyalkyl, alkoxycarbonyl and carbamoyl; l and m may be the same or different and are from 2 to 5; Q and Z may be the same or different and are an O, N or S atom; X and Y may be the same or different and are selected from the group consisting of



wherein R_4, R_5 and R_6 may be the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl, amino, alkylamino, aminoalkyl, and carbamoyl; said method comprising reacting a radionuclide containing solution and a ligand having the general formula:

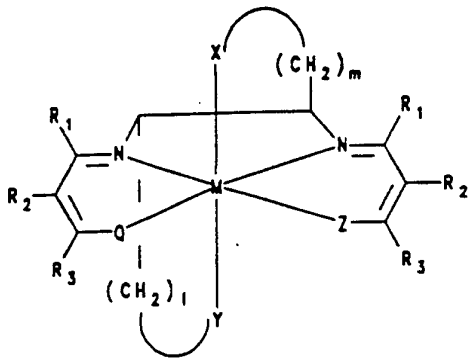


wherein R_1, R_2, R_3, l, m, X, Y, Q, and Z are as defined above.

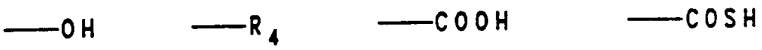
15. A method according to claim 14, wherein either R_1 and R_2, or R_2 and R_3 together may form a carbocyclic or heterocyclic ring of 5 to 7 members.

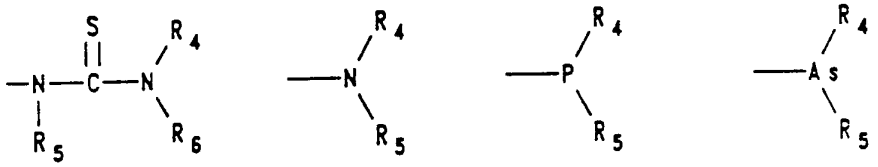
16. A method according to claim 14, wherein M is technetium or rhenium, and said radionuclide containing solution is a pertechnetate or perrheneate solution respectively.

17. A radiographic imaging agent comprising a complex having the general formula:



wherein M is a radionuclide; and wherein R_1, R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly-hydroxyalkyl, mono- or poly- alkoxyalkyl, alkoxycarbonyl and carbamoyl; l and m may be the same or different and are from 2 to 5; Q and Z may be the same or different and are an O, N or S atom; X and Y may be the same or different and are selected from the group consisting of





wherein R_4, R_5 and R_6 may be the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl, amino, alkylamino, aminoalkyl, and carbamoyl; and a pharmaceutically acceptable radiological vehicle.

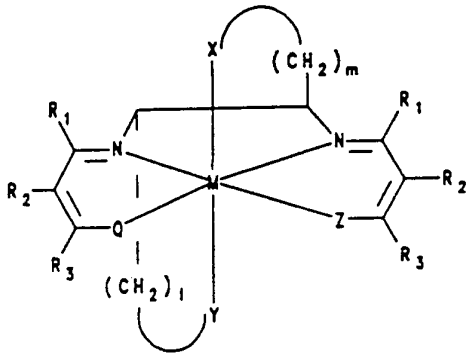
18. An imaging agent according to claim 17, wherein either R_1 and R_2, or R_2 and R_3 together may form a carbocyclic or heterocyclic ring of 5 to 7 members.

19. An imaging agent according to claim 17, wherein M is technetium or rhenium.

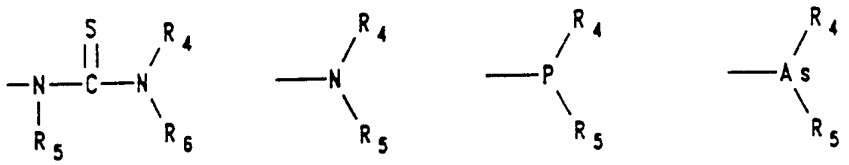
20. An imaging agent according to claim 17, wherein said vehicle is suitable for injection or aspiration and is selected from the group consisting of human serum albumin, aqueous buffer solutions, sterile water, physiological saline, and balanced ionic solutions containing chloride salts, dicarbonate salts or blood plasma cations.

21. An imaging agent according to claim 17, wherein the concentration of said complex in said vehicle is from about 1.0 to 50 millicuries.

22. A method of radiographic imaging, comprising injecting a sufficient amount of an imaging agent to provide adequate imaging and then scanning with a suitable scanning machine; said imaging agent comprising a complex having the general formula:



wherein M is a radionuclide; and wherein R_1, R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly-hydroxyalkyl, mono- or poly- alkoxyalkyl, alkoxycarbonyl and carbamoyl; l and m may be the same or different and are from 2 to 5; Q and Z may be the same or different and are an O, N or S atom; X and Y may be the same or different and are selected from the group consisting of



wherein R_4, R_5 and R_6 may be the same or different and are selected from the group consisting of hydrogen, and organic compounds having 2 to 10 carbon atoms selected from the group consisting of alkyl, aryl, hydroxyl, alkoxyl, mono- or poly- hydroxyalkyl, mono- or poly-alkoxyalkyl, alkoxycarbonyl, amino, alkylamino, aminoalkyl, and carbamoyl; and a pharmaceutically acceptable radiological vehicle.

23. A method of imaging according to claim 22, wherein either R_1 and R_2, or R_2 and R_3 together may form a carbocyclic or heterocyclic ring of 5 to 7 members.

24. A method of imaging according to claim 22, wherein M is technetium or rhenium.

25. A method of imaging according to claim 22, wherein said vehicle is suitable for injection or aspiration and is selected from the group consisting of human serum albumin, aqueous buffer solutions, sterile water, physiological saline, and balanced ionic solutions containing chloride salts, dicarbonate salts or blood plasma cations.

26. A method of imaging according to claim 22, wherein the concentration of said complex in said vehicle is from about 1.0 to 50 millicuries.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/00281

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 49/02; C07F 9/28,

US CL : 424/1.65, 1.77; 534/10, 14; 564/503, 506, 15

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.65, 1.77; 534/10, 14; 564/503, 506, 15; 564/500, 502, 160, 30; 558/158, 230, 6; 562/624, 565, 26; 556/70; 560/169

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Structure Searches

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,&	US, A, 5,243,073 (NEUMANN et al.) 7 September 1993 See the entire document.	1-26
X -- Y	US, A, 3,048,480 (CHURCHILL) 7 August 1962. See column 2, lines 10-20.	1 -- 2
Y	US, A, 5,112,594 (WOULFE et al.) 12 May 1992. See columns 2-4.	1-3, 7-10, 14-26
Y	US, A, 5,112,595 (WOULFE et al.) 12 May 1992. See columns 3 and 4	1-3, 7-10, 14-26
Y	US, A, 4,795,626 (DEUTSCH et al.) 3 January 1989. See columns 5 and 6.	1-3, 7-10, 14-26

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 08 MARCH 1994	Date of mailing of the international search report 04 APR 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer John M. Covert Telephone No. (703) 308-0444

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

Ir. ational application No.
PCT/US94/00281

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,917,879 (DEUTSCH et al.) 17 April 1990. See columns 2 and 3.	1-3, 7-10, 14-26