

Description

This invention relates to radionuclide complexes of ester-substituted diaminedithiols as radiopharmaceuticals, processes for their preparation, kits for the preparation and delivery of the radiopharmaceuticals to target organs for imaging in primates, and methods of using them as diagnostic agents.

BACKGROUND OF THE INVENTION

Radiopharmaceutical compounds have been in use for diagnostic purposes for many years and one skilled in the art of nuclear medicine and radiopharmaceutical research is well aware of the requirements for a diagnostically useful radiopharmaceutical. Briefly, these requirements include: efficient preparation of the radiopharmaceutical, such that preparation in the hospital or pharmacy is possible; efficient transport of the radiopharmaceutical to the target organ; efficient extraction of the radiopharmaceutical by the target organ, such that adequate target to background ratios are achieved to allow diagnostic distinctions; adequate retention in the target organ to allow detection using conventionally available radiation monitoring equipment.

Diaminedithiol complexes of technetium-99m as radiopharmaceuticals have been described previously. Both Burns et al. in European Patent Application 163,119, published December 4, 1985, and Kung et al. in European Patent Application 200,211, published November 5, 1986, describe the use of amine derivatized diaminedithiol complexes of technetium-99m as radiopharmaceuticals useful for determining regional cerebral blood flow. While these complexes have been shown to exhibit adequate uptake into the brains of mammals to provide good target to background ratios, these compounds have shown rather rapid washout from the brain tissue, restricting their usefulness for single photon emission computed tomography with conventionally available equipment.

Lin, U.S. Patent 4,284,619 issued August 18, 1981 describes the use of esters as brain imaging agents. Specifically described are esters of iodinated benzoic acids. These compounds showed very poor brain retention, with the brain to blood ratio at 5 minutes being less than 0.5 in all cases.

Davison et al. in European Patent Appln. No. 135,160, published March 27, 1985, describe the use of a variety of substituted diamidethiol complexes of technetium-99m as renal imaging agents. These diamidethiol ligands result in the formation of anionic complexes with technetium, resulting in high renal extraction, but the anionic charge on these complexes appears to eliminate the potential for adequate brain extraction. Similar anionic complexes are described by Fritzberg, U.S. Patent 4,444,690 issued April 24, 1984; and by Byrne et al., U.S. Patent 4,434,151 issued February 28, 1984; U.S. Patent 4,571,430 issued February 18, 1986; and U.S. Patent 4,575,556 issued March 11, 1986.

Troutner et al. in European Patent Appln. No. 123,504, published October 31, 1984, describe neutral technetium-99m complexes with alkylene amine oximes and their use as radiopharmaceuticals for the evaluation of regional cerebral blood flow. While these compounds have shown adequate brain extraction as well as prolonged retention in the brain of mammals, these complexes convert on standing to a hydrophilic complex which is no longer effective as a radiopharmaceutical for evaluation of regional cerebral blood flow. This conversion with time requires that the radiopharmaceutical be used within 30 minutes after preparation.

Clearly the need exists for more effective radiopharmaceuticals for the evaluation of regional cerebral blood flow which will combine the necessary properties of adequate brain uptake, adequate retention within the brain, distribution in accordance to blood flow, and adequate stability after preparation to be useful in the clinical environment.

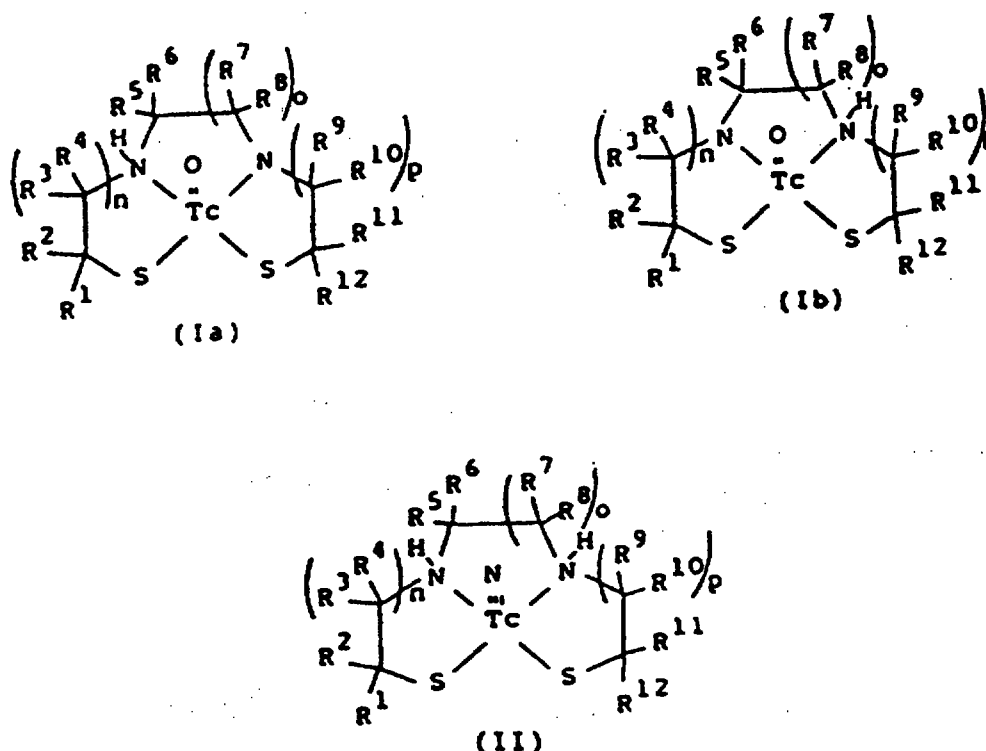
U.S. Patent 2,810,753 issued October 22, 1957, describes di-sulphydryl alkylene diamine polycarboxylic acids as metal ion chelating agent. Some of these acids are immediate precursors to the ester-substituted diaminedithiols of the present invention.

Blondeau et al., *Can. J. Chem.*, 45, 49 (1967), describe the reductive dimerization of thiazolidines to yield N,N'-1,2-ethylenediylbis-L-cysteine derivatives.

A copper complex of N,N'-1,2-ethylenediylbis-L-cysteine, dimethyl ester prepared from the dimethylester dihydrochloride is characterized by Bharadwaj et al., *J. Am. Chem. Soc.*, 108, 1351 (1986).

GB-A-742 996 discloses Di-sulphydryl alkylene diamine polycarboxylic acids and salts thereof.

remain protonated. Thus, when the radionuclide is technetium-99m, the complexes which are obtained are of the general formulas (I) and (II):

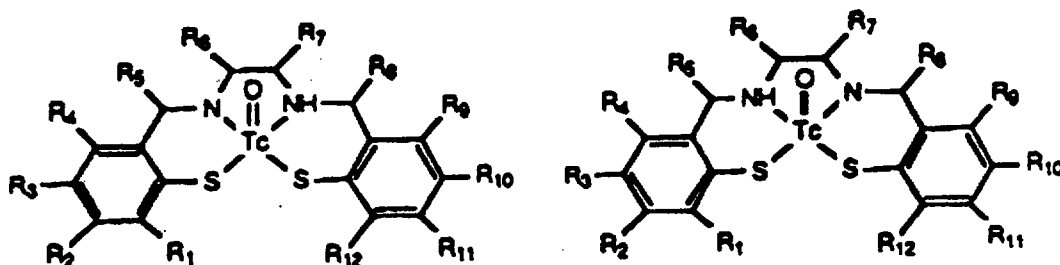


wherein each of R¹ to R¹² individually is selected from the group consisting of H, alkyl of 1-6 carbon atoms and -A-COOR where A is a straight or branched chain alkylene of 0-6 carbon atoms, n, o, p are each independently 1 or 2, and R is alkyl of 1-6 carbon atoms, with the proviso that at least one, but preferably no more than 4, of R¹-R¹² is -A-COOR.

Particularly preferred radiopharmaceuticals are prepared from diaminedithiols where:

- n, o and p are 1; or
- each alkyl of R and R¹-R¹² is from 1-3 carbon atoms; or
- A is a straight chain alkylene of 0-3 carbon atoms, or
- R³ and R¹⁰ are -A-COOR and R⁴ and R⁹ are H; or
- A is a bond, i.e., O, and R is ethyl; or
- A is a bond and stereochemistry at the position where that bond is attached to the diaminedithiol backbone is L(or R-).

Other technetium radiopharmaceuticals within the present invention have the general formulas:



wherein R¹-R¹² are as defined above broadly and preferably.

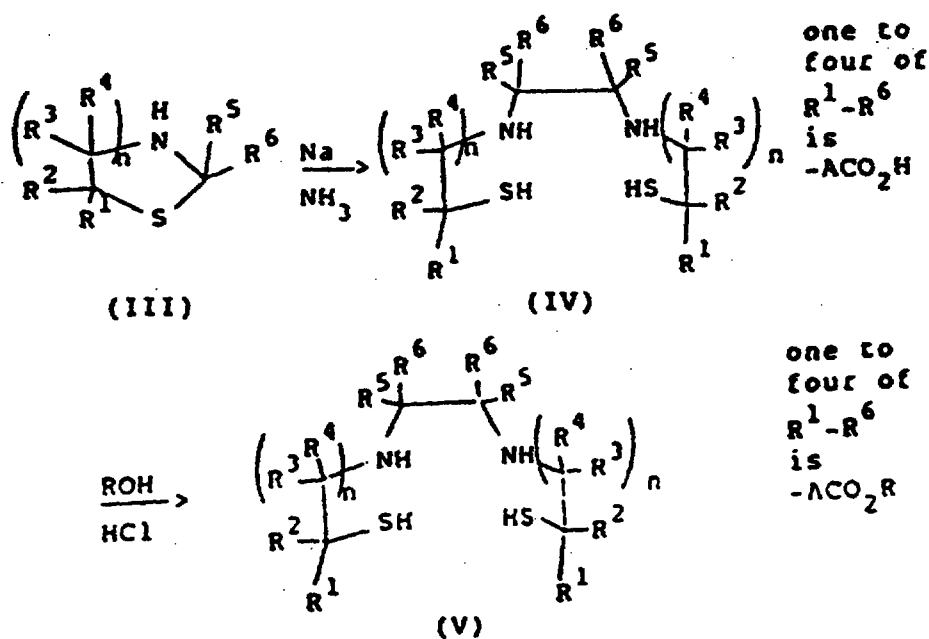
A stannous salt such as stannous glucoheptonate or stannous chloride are preferred reducing agents. Specifically preferred are technetium-99m complexes of (1) N,N'-1,2-ethylenediylbis-L-cysteine, diethyl ester; (2) N,N'-1,2-ethylenediylbis-L-cysteine, dimethyl ester; and (3) N,N'-1,2-ethylenediylbis-L-cysteine, di-n-propyl ester.

DETAILED DESCRIPTION OF THE INVENTION

The diaminedithiol ligands of the present invention can be prepared by several methods of coupling appropriately substituted (and in some cases protected) amine, thiol, and aminethiol fragments. Preparation of the necessary fragments is possible by a wide variety of techniques known to one skilled in the art of organic synthesis. In the following reaction descriptions, R_1 - R_6 are as described above except where stated to the contrary.

The diaminedithiol forming reactions include the reductive dimerization of substituted thiazolidines or a tetrahydro-1,3-thiazene of formula (III) to give the diaminedithiol acids of formula (IV). These can be esterified by reaction of a compound (IV) with an appropriate alcohol and catalyst to afford the ester substituted diaminedithiol of formula (V) (Scheme I). This general synthesis of ester-substituted diaminedithiols has been described by Blondeau et al., *Can. J. Chem.*, 45, 49 (1967).

Scheme I



In particular, a thiazolidine or a tetrahydro-1,3-thiazene of formula (III) can be reacted with sodium in liquid ammonia, followed by esterification with methanol or ethanol using gaseous hydrogen chloride as catalyst to afford a compound of formula (V). Thiazolidines and tetrahydro-1,3-thiazenes of formula (III) are prepared by reaction of an amine-thiol with an aldehyde or ketone. (M. T. Nagasawa et al., *J. Med. Chem.*, 27, 591 (1984)).

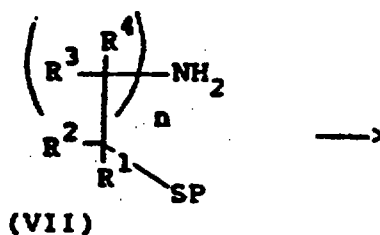
Alternatively, a diaminedithiol can be prepared by the reductive amination of glyoxal or a 1,2-diketone or 1,3-diketone moiety of formula (VI) with an appropriately substituted (and protected) aminethiol of formula (VII) (Scheme II).

In particular, reaction of glyoxal or a ketone moiety with a protected ester aminethiol in the presence of a dehydrating agent

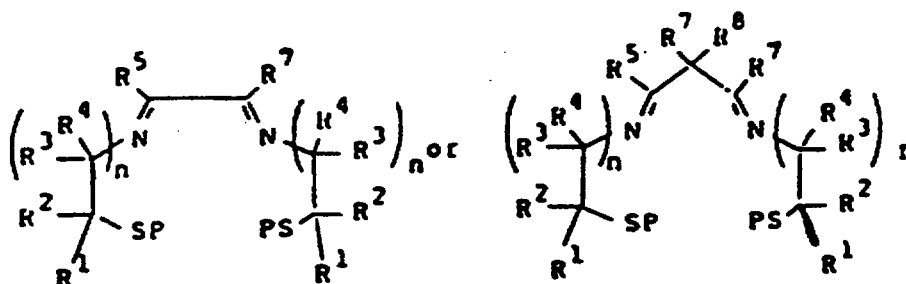
Scheme II



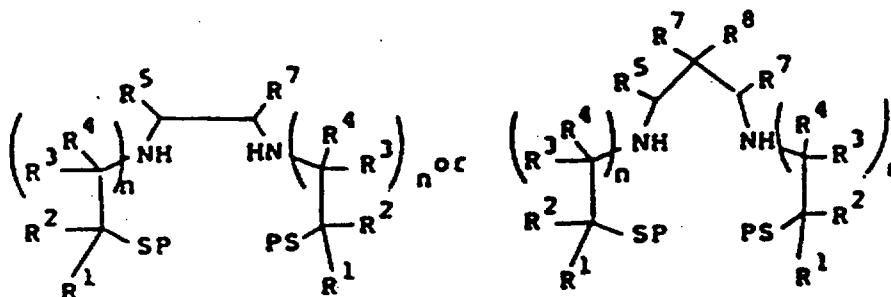
(VI)



(VII)



(VIII)



(IX)

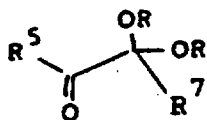
such as a molecular sieve, followed by reduction of the diimine intermediate of formula (VIII) with a borohydride reducing agent affords a protected diaminedithiol of formula (IX). Protecting group P, which can be any of a variety of protecting groups for sulfur, including methoxymethyl, methoxyethoxymethyl, p-methoxybenzyl or benzyl, can be removed by appropriate methods well known to one skilled in the art of

organic synthesis such as trifluoroacetic acid, mercuric chloride, or sodium in liquid ammonia. In the case of Lewis acid labile groups including acetamidomethyl and benzamidomethyl, P can be left intact. Labeling of the ligand with technetium, in the case of Lewis acid labile protecting groups, will cleave the group P, rendering the protected diaminedithiol equivalent to the unprotected form.

- 5 For the preparation of unsymmetrical diaminedithiol ligands, a protected form of a compound of formula (VI), such as (X), can be used in a stepwise coupling sequence shown below (Scheme III).

Scheme III

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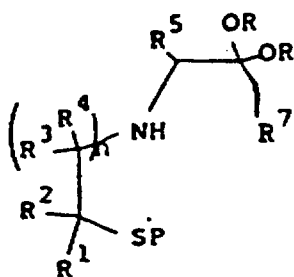
(X)



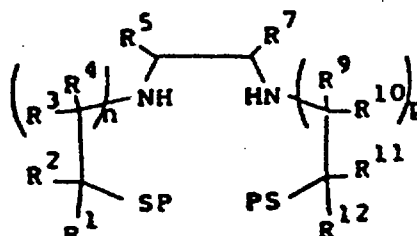
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(XI)

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(XII)



(XIII)

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- A protected aminethiol of formula (VII) is reductively aminated with a compound of formula (X) to afford the protected carbonyl compound of formula (XII). Deprotection, followed by reductive amination with a second aminethiol (VII') affords the unsymmetrical diaminedithiol ligand of formula (XIII), which may be deprotected by an appropriate method, as described above. The reaction conditions are essentially the same as for the reductive amination of Scheme II starting with commercially available reagents or those prepared easily from commercially available reagents.

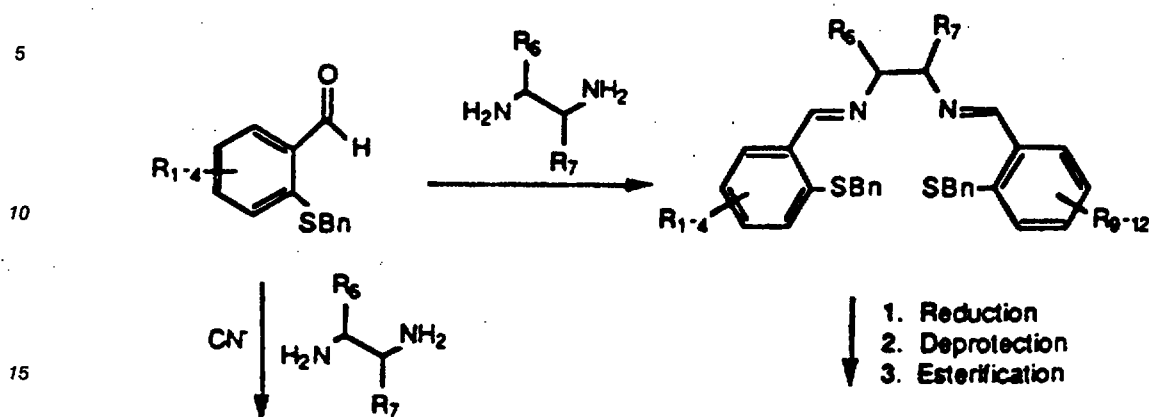
- Aryl-containing diaminedithiols can be prepared by reaction of an appropriate amine with thiol-substituted benzaldehydes, as shown in Scheme IV to afford the diimines. These can then be reduced to the diamine with a reducing agent such as sodium borohydride. Alternatively, the aldehyde, amine and a cyanide nucleophile can be reacted in a Strecker synthesis to prepare the bis-amino-nitrile. Hydrolysis of this compound affords the bis-amino acid. Deprotection of the sulfur by appropriate methods as described

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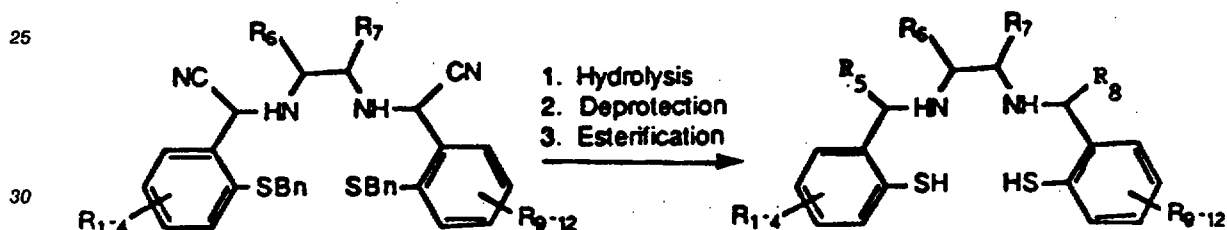
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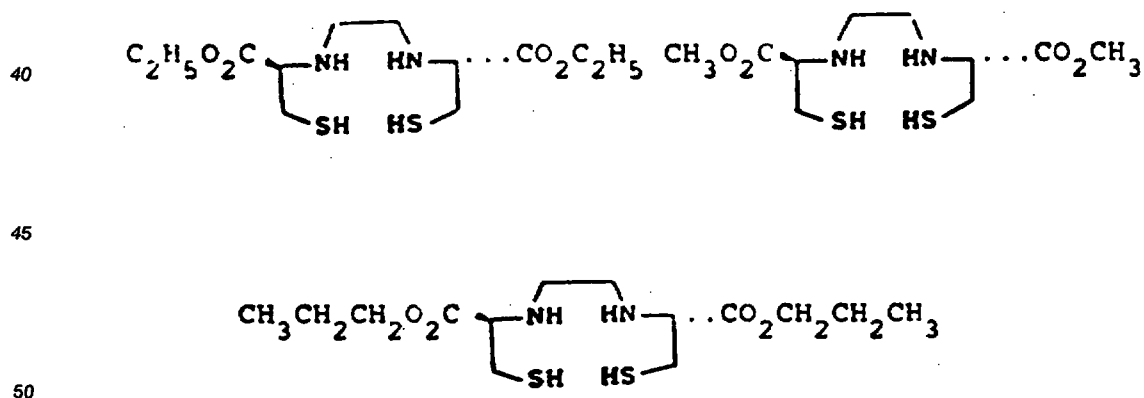
previously is followed by esterification by methods described previously to afford the final compounds.



20 **SCHEME IV (continued)**



35 Particular diaminedithiol esters useful in the practice of this invention have the formulas:



or pharmaceutically suitable salts thereof.

The invention can be further understood by the following examples in which parts and percentages are by weight unless otherwise indicated and temperatures are in degrees centigrade.

EXAMPLE 1

Synthesis of N,N'-1,2-ethylenediylbis-L-cysteine, diethyl ester, dihydrochloride

5 Part A: Synthesis of (R)-thiazolidine-4-carboxylic acid, sodium salt

To (R)-thiazolidine-4-carboxylic acid (45.0 g, 0.338 mol) in 600 mL absolute ethanol was added sodium hydroxide pellets (13.52 g, 0.338 mol). The slurry was stirred until the pellets were dissolved (30-45 min). The ethanol was removed under aspirator on a rotary evaporator, another 300 mL ethanol added and
 10 evaporated, and the remaining white solid placed under high vacuum overnight to remove residual traces of ethanol.

Part B: Synthesis of N,N'-1,2-ethylenediylbis-L-cysteine

15 A three-necked 1000 mL flask, equipped with a gasinlet, mechanical stirrer with glass paddle, and dry ice condenser was cooled to -78° and 450 mL ammonia condensed into the flask. The cooling bath was removed and the solution allowed to warm up for 30min. Sodium spheres (3-8 mm, 14 g, 0.6 mol) were washed with pentane, soaked in 2-propanol for 10 min, and then washed twice more with pentane. The entire amount of thiazolidine sodium salt prepared in Part A above was added to the ammonia in one
 20 portion and fairly rapid stirring begun. The sodium spheres were added, 2-3 at a time, waiting 45-60 sec between additions, until a persistent blue color was obtained for 10 min. The addition took about 45 min and not all of the sodium was used. After 10 min of blue color, the reaction was quenched with solid ammonium chloride, the condenser removed, and the ammonia evaporated under nitrogen with the aid of a warm water bath. The white solid residue was dissolved in 400 mL of water and concentrated HCl added until the pH of
 25 the mixture was 2. The slurry was cooled to 0° for 1 h, then suction filtered through a medium porosity glass frit. The solids were washed with 2 X 200 mL water and dried over calcium sulfate in a dessicator under vacuum until a constant weight was obtained (18-24 h) to yield 31.8 g (70%) of a white powder, m.p. 230-231° (decomposition, although darkening begins at 214-216°). The material was insoluble in all solvents except aqueous base.

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Part C: Synthesis of N,N'-1,2-ethylenediylbis-L-cysteine, diethyl ester, dihydrochloride

N,N'-1,2-ethylenediylbis-L-cysteine from Part B (20.0 g 74.5 mmol) was slurried in 1200 mL absolute ethanol in a 2000 mL three-necked flask equipped with a gas inlet tube (a hollow tapered tube finishing in a
 35 2 mm diameter bore) from an HCl tank, mechanical stirrer, and condenser with gas outlet hooked up to an HCl trapping system. Vigorous stirring was started and HCl gas bubbled in at a rate to maintain a rapid reflux of the ethanol. Gas addition was continued for 1.5 h, then reflux was continued for an additional 2.5 h. The slurry was then cooled to 0° for one hour in an ice bath, suction filtered (Whatman #1, Buchner funnel), and the solids washed with 2 X 100 mL cold ethanol to afford 26.4 g of crude diester (89%) after
 40 drying.

Part of this material was crystallized by slurrying the solids in 650 mL ethanol at 50° with stirring, and adding 80 mL water. The slightly cloudy solution was rapidly suction filtered (Whatman #1), stoppered, and allowed to crystallize in the refrigerator overnight. The material was filtered, washed with 2 X 100 mL cold ethanol, and dried under vacuum in a dessicator to yield 19.56 g (67%), m.p. 182° (decomposition with
 45 melting).

Part D: Purification of N,N'-1,2-ethylenediylbis-L-Cysteine, diethyl ester, dihydrochloride (This step was performed under GMP conditions, using approved solvents and reagents, and specially prepared glassware and equipment)

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Sodium Carbonate (58.38 g, 0.55 mol) was dissolved in 1200 mL of deoxygenated sterile water with mechanical stirring under a nitrogen atmosphere. N,N'-1,2-ethylenediylbis-L-Cysteine, diethyl ester, dihydrochloride (175 g, 0.44 mol) was added to this solution, followed by diethyl ether (400 mL). The solution was stirred for 15 minutes, and the pH adjusted to 8.5-9.0 by the addition of more sodium
 55 carbonate, if necessary. The solution was poured into a separatory funnel and the layers separated. The aqueous portion was extracted with 4x200 mL of diethyl ether. The combined ether extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure on a rotary evaporator.

A solution of absolute ethanol (4300 mL), sterile water (520 mL), and conc. hydrochloric acid (103 g) was heated, with stirring, to 70°. The concentrated residue was added to this solution, and the flask which contained the residue was rinsed out with 2x300 mL ethanol, which was then also added to the hot solution. Heating was continued until the solution was clear, at which time it was rapidly suction filtered through a glass fibre filter (Whatman GF/D). The flask which contained the solution was rinsed with 2x300 mL ethanol, which was also passed through the filter. The filtered solution was stoppered and stored at 0° for 24 hours. The resulting crystalline material was suction filtered (Whatman #1), washed twice with ethanol, twice with diethyl ether, and dried under vacuum to obtain a highly purified, pharmaceutically acceptable form of N,N'-1,2-ethylenediylbis-L-Cysteine, diethyl ester, dihydrochloride. Yield is 140 g (80%), m.p. 182-185° (decomposition).

EXAMPLE 2

Synthesis of N,N'-1,2-ethylenediylbis-L-cysteine, dimethyl ester, dihydrochloride

N,N'-ethylenediylbis-L-cysteine prepared as in Example 1, Part B (15.0 g, 0.56 m) was slurried in 500 mL of methanol and hydrogen chloride gas was bubbled in at a vigorous rate to maintain the methanol at reflux and to dissolve the solids. After one hour of gas addition, the solution was refluxed an additional two hours. Cooling on ice for one hour resulted in crystallization. Filtration and drying afforded 9.4 g (47%) of the dimethylester dihydrochloride, m.p. 188°. Purification of this material can be accomplished as described in Example 1, Part D.

EXAMPLE 3

Synthesis of N,N'-1,1-ethylenediylbis-D-(S-benzamidomethyl)penicillamine, dimethyl ester, dihydrochloride

Part A: Synthesis of S-benzamidomethyl-(S)-penicillamine methyl ester

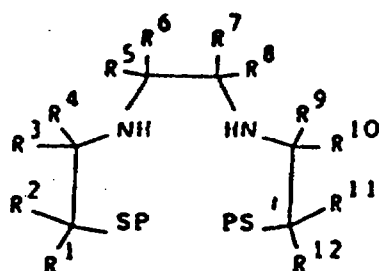
(S)-Penicillamine methyl ester hydrochloride (1.0 g, 5.0 mmol) was dissolved in neat trifluoroacetic acid (5 mL) under nitrogen. Benzamidomethanol (0.76 g, 5.0 mmol) was added and the solution stirred for one hour at 25°. The solvent was evaporated on a rotary evaporator to give the desired product as a crystalline trifluoroacetate salt. This was not further purified, but converted directly into the free base. The solid was dissolved in water (10 mL) and saturated sodium bicarbonate solution added until gas evolution ceased and pH > 8.5. The aqueous solution was extracted with ethyl acetate (2 x 15 mL), and extracts dried over sodium sulfate, filtered, and evaporated to yield 0.62 g (42%) of the product as a clear oil.

Part B: Synthesis of N,N'-1,2-ethylenediylbis-D-(S-benzamidomethyl)penicillamine, dimethyl ester, dihydrochloride

S-benzamidomethyl-(S)-penicillamine methyl ester (0.3 g 1.0 mmol) was placed in a flask with 3 mL of ethanol under nitrogen. Molecular sieves (10 -12, 3A) were placed in the flask and glyoxal (40% aqueous solution, 73 mg, 0.5 mmol) was added. The reaction was stirred overnight at room temperature and then three hours at 40°, at which time the resulting slurry was filtered and sodium cyanoborohydride (1.29 g, 2.05 mmol) added to the filtrate. After stirring for 4 h at room temperature, the solvent was evaporated and the residue dissolved in water (20 mL) and extracted with ethyl acetate (3 x 15 mL). This resulting solution was dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (70:30 ethyl acetate:hexane) and the appropriate fractions (determined by TLC) were evaporated. Treatment with ethanolic hydrogen chloride until pH > 1 followed by evaporation yielded 80 mg (23%) of the product as a white solid, m.p. 142-145°.

Using the synthesis procedures described above, the diaminedithiols of Examples 1-3 and other diaminedithiol compounds which can be prepared are shown in Table 1.

Table 1



Ex. No.	Stereo-Chem.	m.p. °C	R ¹	R ²	R ³	R ⁴	R ⁵
1	L,L	182	H	H	CO ₂ C ₂ H ₅	H	H
2	L,L	188	H	H	CO ₂ CH ₃	H	H
3	D,D	142-145	CH ₃	CH ₃	CO ₂ CH ₃	H	H
4	D,D	115-119	CH ₃	CH ₃	CO ₂ C ₂ H ₅	H	H
5	L,L	160-164	H	H	CO ₂ C ₃ H ₇	H	H
6	L,L		H	H	CO ₂ C ₄ H ₉	H	H
7	D,D	182-185	H	H	CO ₂ C ₂ H ₅	H	H
8	L,L		H	H	CO ₂ C ₂ H ₅	H	CH ₃
9	mix	104-105	H	H	CO ₂ C ₂ H ₅	H	CO ₂ C ₂ H ₅
10	mix	145-146	H	H	H	H	CO ₂ C ₂ H ₅
11	mix		CH ₃	CH ₃	H	H	CO ₂ C ₂ H ₅
12	L,L		H	H	CH ₂ CO ₂ C ₂ H ₅	H	H
13	mix		H	H	(CH ₂) ₃ CO ₂ C ₂ H ₅	H	H
14	mix		C ₆ H ₁₃	C ₆ H ₁₃	CO ₂ CH ₃	H	H

Table 1 (continued)

Ex. No.	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹	R ¹²	P
1	H	H	H	H	CO ₂ C ₂ H ₅	H	H	H
2	H	H	H	H	CO ₂ CH ₃	H	H	H
3	H	H	H	H	CO ₂ CH ₃	CH ₃	CH ₃	BZM*
4	H	H	H	H	CO ₂ C ₂ H ₅	CH ₃	CH ₃	BZM*
5	H	H	H	H	CO ₂ C ₃ H ₇	H	H	H
6	H	H	H	H	CO ₂ C ₄ H ₉	H	H	H
7	H	H	H	H	CO ₂ C ₂ H ₅	H	H	H
8	H	CH ₃	H	H	CO ₂ C ₂ H ₅	H	H	BZM*
9	H	CO ₂ C ₂ H ₅	H	H	CO ₂ C ₂ H ₅	H	H	H
10	H	CO ₂ C ₂ H ₅	H	H	H	H	H	H
11	H	H	H	H	H	CH ₃	CH ₃	H
12	H	H	H	H	CH ₂ CO ₂ C ₂ H ₅	H	H	H
13	H	H	H	H	(CH ₂) ₃ CO ₂ C ₂ H ₅	H	H	H
14	H	H	H	H	CO ₂ CH ₃	C ₆ H ₁₃	C ₆ H ₁₃	H

Table 1 (continued)

Ex. No.	Stereo- Chem.	m.p. °C	R ¹	R ²	R ³	R ⁴	R ⁵
15	L,L		H	H	CO ₂ C ₂ H ₅	H	H
16	L,L		H	H	CO ₂ C ₂ H ₅	H	CH ₃
17	mix		CO ₂ C ₂ H ₅	H	H	H	H
18	L,L		H	H	H	(CH ₂) ₆ CO ₂ CH ₃	H
19	L,L		CH ₃	CH ₃	CO ₂ C ₂ H ₅	H	H
20	L,L		H	H	CO ₂ iC ₃ H ₇	H	H
21	L,L		H	H	CO ₂ CH ₂ C(CH ₃) ₃	H	H
22	L,L		H	H	CO ₂ CH ₂ CH(CH ₃) ₂	H	H
23	L,L		H	H	CO ₂ (CH ₂) ₄ CH ₃	H	H
24	L,L		H	H	H	CO ₂ CH ₃	(CH ₂) ₉ CH ₃
25	L,L		H	H	H	(CH ₂) ₉ CO ₂ CH ₃	H
26	mix		H	H	H	H	H
27	L,L		H	H	H	CO ₂ CH ₂ C ₆ H ₅	H
28	L,L		H	H	H	CO ₂ (p-NO ₂ C ₆ H ₅)	H
29	L,L		H	H	H	CO ₂ C ₆ H ₅	H
30	mix		H	H	H	H	H
31	L,L		H	H	H	CO ₂ (3,4,5-C ₆ H ₂ F ₃)	H

Table 1 (continued)

Ex. No.	6 R	7 R	8 R	9 R	10 R	11 R	12 R	P
15	H	H	H	H	H	H	H	BZM
16	CH ₃	CH ₃	H	H	CO ₂ C ₂ H ₅	H	H	H
17	H	H	H	H	H	H	CO ₂ C ₂ H ₅	H
18	H	H	H	(CH ₂) ₆ CO ₂ CH ₃	H	H	H	H
19	H	H	H	CO ₂ C ₂ H ₅	H	CH ₃	CH ₃	BZM
20	H	H	H	CO ₂ C ₃ H ₇	H	H	H	H
21	H	H	H	CO ₂ CH ₂ C(CH ₃) ₃	H	H	H	H
22	H	H	H	CO ₂ CH ₂ CH(CH ₃) ₂	H	H	H	H
23	H	H	H	CO ₂ (CH ₂) ₄ CH ₂	H	H	H	H

Table 1 (continued)

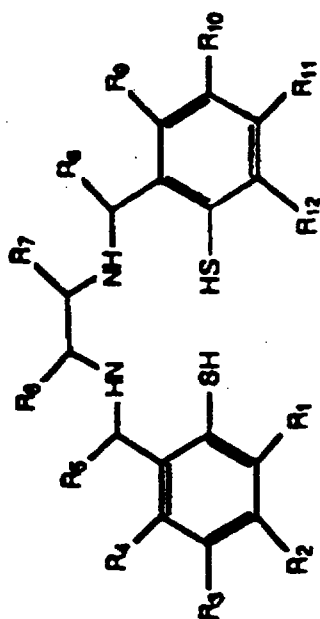
Ex. No.	6 R	7 R	8 R	9 R	10 R	11 R	12 R	P
24	H	H	H	H	CO ₂ CH ₃	H	H	BZM*
25	H	H	H	H	(CH ₂) ₉ CO ₂ CH ₃	H	H	H
26	CO ₂ (CH ₂) ₉ CH ₃	H	H	H	H	H	H	BZM*
27	H	H	H	H	CO ₂ CH ₂ C ₆ H ₅	H	H	H
28	H	H	H	H	CO ₂ (2-NO ₂ C ₆ H ₅)	H	H	H
29	H	H	H	H	CO ₂ C ₆ H ₅	H	H	H
30	CO ₂ (4-C ₅ H ₄ N)	H	H	H	H	H	H	BZM*
31	H	H	H	H	CO ₂ (3,4,5-C ₆ H ₂ F ₃)	H	H	H

BZM = Benzamidomethyl

Using the synthesis procedure set forth in

Scheme IV, other diaminedithiols which can be prepared are shown in Table 2.

Table 2

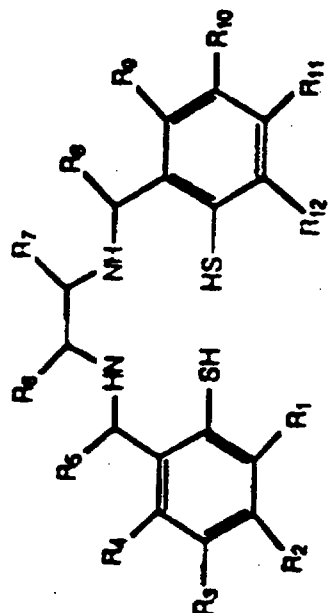


Ex No.	Stereo Chem.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
32	mix	H	H	H	H	CO ₂ CH ₃	H
33	.	CO ₂ C ₆ H ₅	H	H	H	H	H
34	.	H	CH ₂ CO ₂ CH ₃	H	H	H	(CH ₂) ₃ CH ₃
35	.	H	H	CO ₂ CH ₂ C ₆ H ₅	H	H	H
36	.	H	H	H	(CH ₂) ₆ CO ₂ CH ₃	H	H
37	mix	H	H	CO ₂ CH ₃	H	CO ₂ CH ₃	H

Table 2 (continued)

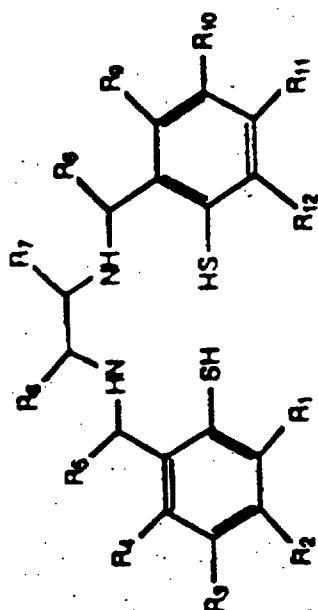
Ex No.	Stereo Chem.	B ¹	B ²	B ³	B ⁴	B ⁵	B ⁶
38	mix	H	H	(CH ₂) ₂ CH ₃	H	H	CO ₂ CH ₃
39	mix	H	H	H	H	H	CO ₂ CH ₃
40	-	H	H	(CH ₂) ₁₀ CO ₂ CH ₃	H	H	H
41	mix	H	H	H	H	CO ₂ C ₆ H ₅	H
42	mix	H	H	H	H	CO ₂ (p-NO ₂ C ₆ H ₄)	H
43	mix	CH ₃	H	CH ₃	H	CO ₂ (4-C ₅ H ₄ N)	H
44	mix	H	H	H	H	H	CO ₂ (CH ₂) ₉ CH ₃

Table 2 (continued)



C	$\overline{R^7}$	$\overline{R^8}$	$\overline{R^9}$	$\overline{R^{10}}$	$\overline{R^{11}}$	$\overline{R^{12}}$
32	H	CO ₂ CH ₃	H	H	H	H
33	H	H	H	H	H	CO ₂ C ₂ H ₅
34	(CH ₂) ₃ CH ₃	H	H	H	CH ₂ CO ₂ CH ₃	H
35	H	H	H	CO ₂ CH ₂ C ₆ H ₅	H	H
36	H	H	(CH ₂) ₆ CO ₂ CH ₃	H	H	H
37	H	CO ₂ CH ₃	H	CO ₂ CH ₃	H	H

Table 2 (continued)



R_7	R_8	R_9	R_{10}	R_{11}	R_{12}
38	H	H	$(CH_2)_2CH_3$	H	H
39	CO_2CH_3	H	H	H	H
40	H	H	$(CH_2)_{10}CO_2CH_3$	H	H
41	H	$CO_2C_6H_5$	H	H	H
42	H	$CO_2(p-NO_2C_6H_5)$	H	H	H
43	H	$CO_2(4-C_5H_4N)$	CH_3	H	CH_3
44	H	H	H	H	H

The radiopharmaceutical complexes of the present invention can easily be prepared by admixing a salt of a radioactive metal and the diaminedithiol ligand in the presence of a suitable reducing agent, if required, in aqueous media at temperatures from room temperature to reflux temperature or even higher, and are obtained and isolatable in high yield at both macro (carrier added, e.g., ^{99}Tc) concentrations and at tracer (no carrier added, e.g., ^{99m}Tc) concentrations of less than 10^{-6} molar. In some cases the diaminedithiol ligand may itself act as the reducing agent thus eliminating the need for an additional reducing agent. Suitable additional reducing agents, when required or desired are well known to those skilled in the art. The reaction is generally complete after 1 minute to 2 hours, depending upon the identity of the particular reagents employed. The radiolabelled complex is made in the same way as any corresponding non-radioactive diaminedithiol complex by simply substituting the desired radionuclide for the corresponding non-radioactive element in the starting materials, except in the case of technetium because all technetium isotopes are radioactive.

In the case of technetium such as, for example ^{99}Tc or ^{99m}Tc , a complex in accord with this invention is preferably made by mixing pertechnetate (Tc^{+7}) with the desired diaminedithiol in aqueous medium, then adding to the reaction mixture an appropriate reducing agent capable of reducing the technetium. Among suitable reducing agents are alkali metal dithionites, stannous salts, sodium borohydride, and others, as is well known.

The diaminedithiol technetium complexes of this invention can also be prepared from preformed technetium complexes by treating these preformed complexes with an excess of ligands under suitable conditions. For example, the technetium-diaminedithiol complex can also be prepared by reacting the desired diaminedithiol ligand with the tetrahalo-oxo complex of Tc^{+5} or with a technetium-glucoheptonate complex, or the like.

An excess of the diaminedithiol ligand, up to 50 to 100 fold molar excess or more, and an excess of reducing agent, can be used in the complexing reaction to ensure maximum yield from the technetium. Following the reaction, the desired complex can be separated from the reaction mixture, if required, by crystallization or precipitation or by conventional chromatography.

5 Kits in accord with the present invention comprise a sterile, non-pyrogenic, diaminedithiol ligand and, if required, a quantity of a reducing agent for reducing a preselected radionuclide. Preferably, such kits contain a predetermined quantity of a sterile diaminedithiol ligand and a predetermined quantity of a sterile reducing agent capable of reducing a predetermined quantity of the preselected radionuclide. It is also preferred that the diaminedithiol ligand and reducing agent be lyophilized, when possible, to facilitate
10 storage stability. If lyophilization is not practical, the kits can be stored frozen or in solution at room temperature. The choice of radionuclides will in general be dependent on the final use of the labeled product. Of course, because of the availability of technetium-99m generators, such a radionuclide is especially preferred.

In one embodiment of the invention, a kit for use in making the complexes of the present invention from
15 a supply of ^{99m}Tc such as the pertechnetate solution in isotonic saline available in most clinical laboratories includes the desired quantity of a selected ligand to react with a selected quantity of pertechnetate, and a reducing agent such as stannous chloride in an amount sufficient to reduce the selected quantity of pertechnetate to form the desired complex.

A preferred kit for the facile preparation of the desired Tc-99m radiopharmaceutical, in accordance with
20 the present invention, is comprised of two vials. One vial (A) contains the ester derivatized diaminedithiol ligand prepared in lyophilized form at acidic pH, where ligand stability is optimal, and an inert filler, such as mannitol, to provide easy lyophilization. The second vial (B) contains a reductant suitable to convert the ^{99m}Tc to the desired oxidation state and an inert filler such as mannitol. The second vial is lyophilized at a pH of approximately 9. When the contents of the vials are mixed together with sterile saline, an optimal pH
25 ~3.0-5.0 is obtained. This provides optimal reaction of the diaminedithiol ligand with the reduced ^{99m}Tc to prepare the desired radiopharmaceutical in high yield and high purity. One method by which the Tc-99m radiopharmaceutical can be prepared in high yield is as follows:

One vial (A) is prepared as a sterile, non-pyrogenic, freeze-dried material containing the dihydrochloride salt of the ester-derivatized diaminedithiol ligand at levels of 100 μg to 2 mg, or higher, with a suitable inert filler
30 such as mannitol, to provide a suitable plug after freeze-drying.

The second vial (B) is prepared as a sterile, non-pyrogenic, freeze-dried material containing a suitable reductant, such as a stannous salt (e.g., SnCl_2) at levels of 5 μg to 100 μg , or more. Vial B may also contain a ligand to stabilize Sn(II) , such as ethylene diamine tetraacetic acid (EDTA) at a level of 100 μg to 1.0 mg, or more. In addition, a bulking agent such as mannitol may be used to aid in lyophilization.

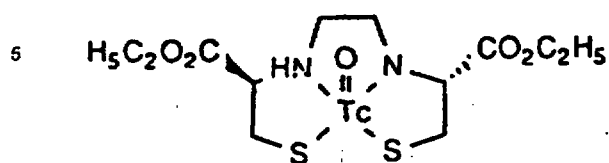
35 The ^{99m}Tc radiopharmaceutical, as described in the present invention, is prepared by admixing the contents of vials (A) and (B) with $^{99m}\text{TcO}_4$ from a $^{99}\text{Mo}/^{99m}\text{Tc}$ radiopharmaceutical generator using sterile techniques well known to those skilled in the art of preparing sterile injectable materials. The generator eluant added should provide about 20-50 mCi of activity. After 15 minutes at room temperature, the ^{99m}Tc diaminedithiol complex, as described herein, is formed in high radiochemical yield (e.g., >80%).
40

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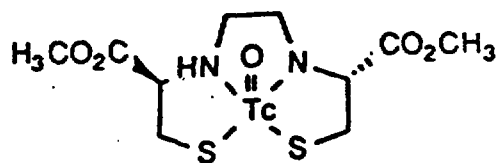
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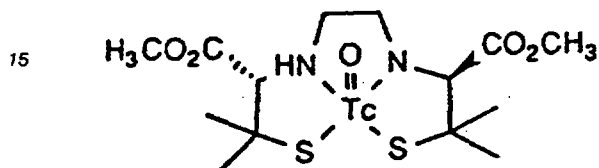
The following examples illustrate the preparation of technetium-99m complexes of the present invention.



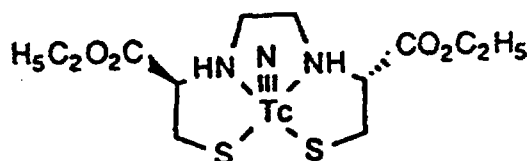
10 Example A



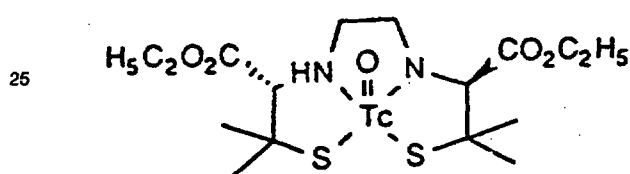
Example B



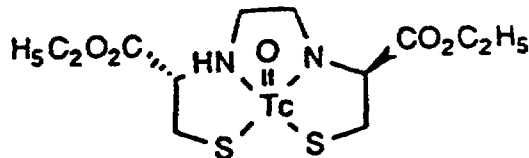
20 Example C



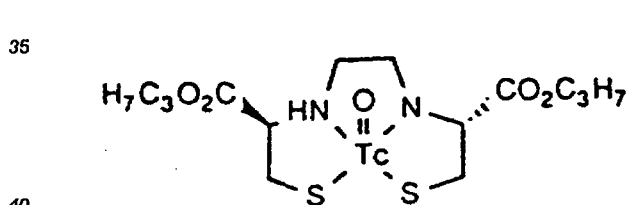
Example D



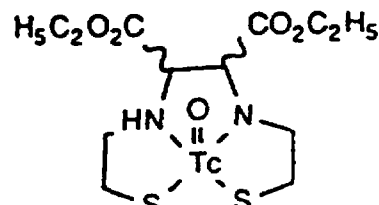
30 Example E



Example F



40 Example G



Example H

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These technetium-99m complexes were prepared using standard labeling conditions similar to those reported in the literature for other diaminedithiol ligands. For all of the complexes except the complex of Example D, a Glucoscan™ kit (a mixture of sodium glucoheptonate and stannous chloride) was reconstituted with 50-150 mCi of ^{99m}TcO₄ obtained by elution of a ⁹⁹Mo/^{99m}Tc radionuclide generator. The diaminedithiol (1-10 mg) in water (0.2-1.0 mL) was added and the mixture allowed to stand for 1 to 30 minutes. In the case of the complexes of Examples C, E and I, warming was necessary to effect removal of the benzamidomethyl protecting groups. For the complex of Example D, a modification of the procedure of Baldas et al., *Int. J. Appl. Radiat. Isot.*, 36, 133 (1985) was used. Generator eluate (100-200 mCi) was reduced to dryness by rotary evaporation and 15 mL 12 M HCl followed by 15 mg sodium azide were added with stirring. After standing for 5 minutes, the mixture was reduced to dryness by rotary evaporation and redissolved in 1 mL buffer (0.05 M sodium phosphate, pH 7.0). The diaminedithiol (1-10 mg) in 0.2-2 mL saline was added to the residue from above and the mixture was allowed to stand at room temperature for 1 to 30 minutes, warming if necessary to complete the reaction.

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Once the complexes were prepared, they were purified by high pressure liquid chromatography on a Brownlee RP-8 Spheri 5 column using a 0.05 M ammonium acetate (NH_4OAc)/methanol gradient. The gradient typically ran from 20 - 40% methanol initially up to 100% methanol over 15 minutes and included an initial hold period at the start of the gradient of 1-10 minutes, and the purified complexes were isolated by rotary evaporation of the solvent at room temperature. The complexes obtained in this fashion were evaluated for purity by thin layer chromatography on Whatman C-18 reversed-phase plates using a solvent mixture containing 65% methanol, 5% tetrahydrofuran, 10% acetonitrile, and 20% 0.5 M NH_4OAc . In all cases, radiochemical purity was greater than 90%. Solutions of the complexes in saline were shown to be stable for at least 4 hours.

The complexes are injected intravenously, usually in saline solution, at a dose of 5 to 100, preferably 5 to 50 millicuries per 70 kg of body weight and imaging is conducted by known procedures.

UTILITY

The above-described complexes were evaluated for potential clinical utility as radiopharmaceuticals for the evaluation of regional cerebral blood flow by performing brain imaging studies in rhesus monkeys. From these studies, brain extraction (% injected dose), and brain retention ($T_{1/2}$) were determined.

METHODS

Male rhesus monkeys were food deprived for 24 hours prior to induction of anesthesia with an intramuscular injection of a mixture of Ketamine hydrochloride (10 mg/kg) and Acepromazine maleate (1 mg/kg). Subsequent injections of sodium pentobarbital (65 mg/mL) via an external saphenous vein catheter were given to maintain anesthesia. Immediately prior to imaging, 18-22 mCi of the technetium-99m complex were administered via the saphenous vein catheter.

Dynamic planar imaging was performed using a Picker Digital Dyna Camera (Picker Int., Northford, Ct.) interfaced to a Computer Design and Applications (CDA) Microdelta nuclear medicine computer (CDA, Waltham, MA). The animal to be imaged was secured on a patient pallet with its head in the left lateral position in the center of the camera's field of view. Data was acquired dynamically into a 64 x 64 word mode matrix, one frame per minute for up to two hours, using a zoom mode of 2X.

Time-activity curves were acquired using a region of interest (ROI) that enclosed the brain as defined by an isocontour marking a count density change of between 25 and 45 percent of the maximum. A background ROI was placed just outside the occipital area of the brain and followed the contour of the brain ROI. The number of counts per pixel in each ROI per mCi injected was calculated for each of the one minute images in the experiment. The counts in both ROIs are decay corrected and the background counts subtracted from the brain ROI counts.

The percent injected dose (%I.D.) was calculated using the results of the time-activity curves. The peak counts per pixel per mCi were converted to peak disintegrations per minutes. The number of disintegrations in the brain were converted to mCi in the brain and compared to the injected dose, giving a %I.D. in the brain.

The retention time of the complex in the brain is described by the half-life ($t_{1/2}$). Half-life calculations were performed using a commercially available exponential stripping package and a non-linear pharmacokinetic modeling program (Statistical Consultants, Inc. (1986) "PCNONLIN and NONLIN84: Software for the Statistical Analysis of Nonlinear Models" The American Statistician, Vol. 40, 52). Initial estimates of washout rates were determined using the exponential stripping package. These estimates were used in the PCNONLIN modeling program for the determination of washout kinetics and biological $T_{1/2}$. It was assumed that the complexes followed one compartment kinetics. If the data did not support this assumption, then multicompartmental analysis was applied.

The results are shown in Table II.

Table II

CHEMICAL AND BIOLOGICAL CHARACTERISTICS PARTITION COEFFICIENT, BRAIN EXTRACTION AND RETENTION OF ^{99m} Tc COMPLEXES			
EX. NO.	PARTITION COEFFICIENT ¹	MONKEY IMAGING	
		% I.D. ²	T 1/2 (min) ³
A	44	4.8±.8 (6)	>1440 (6)
B	7	2.9±2.4 (5)	167±15 (3)
C	35	3.0 (1)	<30 (1)
D	12	2.8±0.2 (2)	>1440 (2)
E	142	3.2 (1)	<30
F	52	3.2 (2)	<30
G	310	4.6±0.6 (3)	>1440
H	19	<2 (1)	<30
All values are Mean ± SEM			
Value in parenthesis is the number of animals used in the calculation.			

1 Octanol/water partition coefficient.

2 Maximum %I.D. as determined by planar imaging.

3 Estimated half-life of brain clearance.

Another important criteria for a radio-pharmaceutical for the evaluation of regional cerebral blood flow is that the radiopharmaceutical be distributed as a function of blood flow. Distribution as a function of blood flow can be demonstrated from analysis of SPECT images.

Formatted SPECT images were analyzed using a densitometric video based camera system (Loats® Assoc., Westminster, MD) in order to obtain information about the concentration and distribution pattern of ^{99m}Tc. Radioactivity in various brain areas were assumed to be positively and linearly related to changes in film absorbance. Brain area mean absorbance per pixel value was calculated. Neuroanatomical landmarks for placement of brain area ROI were based on human brain positron emission tomography atlases. Ratios of absorbance between different gray matter areas (cortical areas and thalamus) and a white matter reference area were determined at about 50 and 150 minutes post-administration.

This analysis was performed using the complex of Example A. The results are summarized in Table III, and show that a gray/white ratio of 2-3:1 is observed for the complex of Example A, consistent with distribution as a function of cerebral blood flow.

TABLE III

MONKEY BRAIN AREA ACTIVITY RATIOS DERIVED FROM FORMATED SPECT IMAGES OF THE COMPLEX OF EXAMPLE A		
Regions	Time Post compound Administration (min)	
	53	150
Occipital Cortex	3.3	2.6
Parietal Cortex	3.1	2.5
Frontal Cortex	2.9	2.3
Thalamus	2.5	2.1
Values are percent absorbance ratio for regions of interest to the corpus callosum-lateral ventricular (ie. white matter reference area).		

The diaminedithiol radiolabelled complexes, particularly those labelled with Tc-99m, are also useful in labeling white blood cells in vitro.

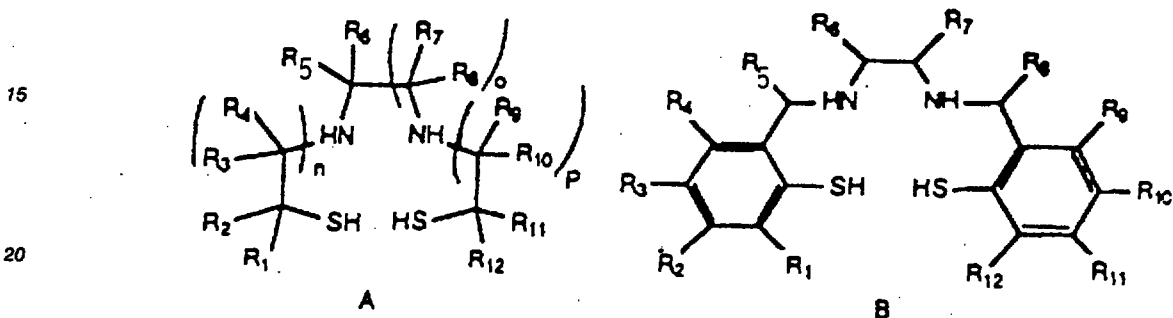
While the diaminedithiol complexes specifically described herein are particularly beneficial in radioimaging brain perfusion in mammals, aminated (N-containing) groups and other groups described in the art, and other unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

5

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

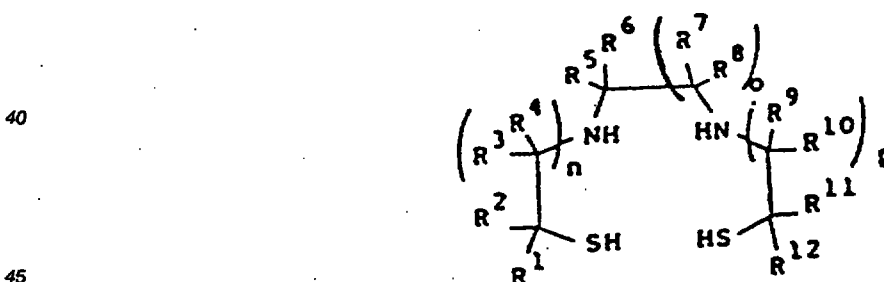
- 10 1. An ester-substituted diaminedithiol of the formula:



or a pharmaceutically suitable salt thereof wherein:

- 25 each of R₁-R₁₂ individually is selected from the group consisting of H, alkyl of 1-10 carbon atoms and -A-COOR wherein A is a straight or branched chain alkylene of 0-10 carbon atoms, n, o, and p are independently 1 or 2, and R is (a) alkyl of 1-10 carbon atoms, (b) phenyl or benzyl optionally substituted with up to 5 ring substituents each selected from alkyl of 1-4 carbon atoms, fluoro, chloro, bromo, nitro, alkoxy of 1-4 carbon atoms, carboxyl, or a carboxylic acid ester of 1-4 carbon atoms, or
30 (c) a 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O or S, with the proviso that at least one of R₁-R₁₂ is -A-COOR, said ester-substituted diaminedithiol in sterile, pharmaceutically acceptable form.

- 35 2. An ester-substituted diaminedithiol of the formula:



or a pharmaceutically suitable salt thereof

- 50 wherein each of R¹-R¹² individually is selected from the group consisting of H, alkyl of 1-6 carbon atoms and -A-COOR wherein A is a straight or branched chain alkylene of 0-6 carbon atoms, n, o and p are independently 1 or 2, and R is alkyl of 1-6 carbon atoms, with the proviso that at least one of R¹-R¹² is -A-COOR, said ester-substituted diaminedithiol in sterile, pharmaceutically acceptable form.

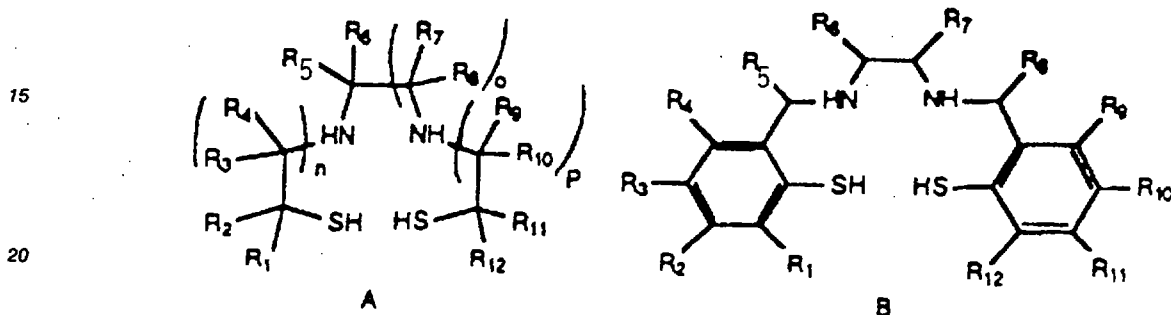
- 55 3. A diaminedithiol of Claim 2 wherein R and any alkyl in R¹-R¹² is from 1-3 carbon atoms.
4. A diaminedithiol of Claim 2 wherein A is a straight chain alkylene of 0-3 carbon atoms.

While the diaminedithiol complexes specifically described herein are particularly beneficial in radioimaging brain perfusion in mammals, aminated (N-containing) groups and other groups described in the art, and other unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

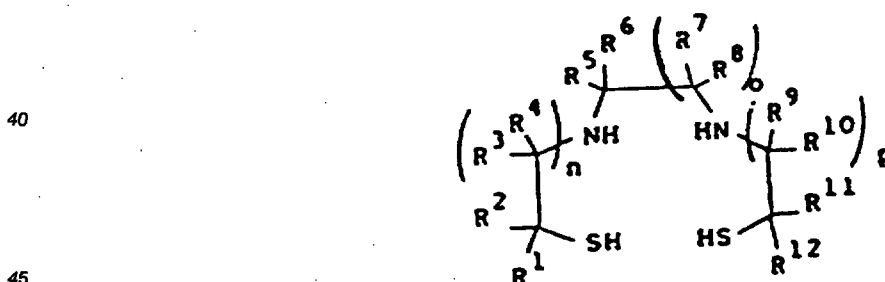
- 10 1. An ester-substituted diaminedithiol of the formula:



or a pharmaceutically suitable salt thereof wherein:

- each of R₁-R₁₂ individually is selected from the group consisting of H, alkyl of 1-10 carbon atoms and -A-COOR wherein A is a straight or branched chain alkylene of 0-10 carbon atoms, n, o, and p are independently 1 or 2, and R is (a) alkyl of 1-10 carbon atoms, (b) phenyl or benzyl optionally substituted with up to 5 ring substituents each selected from alkyl of 1-4 carbon atoms, fluoro, chloro, bromo, nitro, alkoxy of 1-4 carbon atoms, carboxyl, or a carboxylic acid ester of 1-4 carbon atoms, or (c) a 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O or S, with the proviso that at least one of R₁-R₁₂ is -A-COOR, said ester-substituted diaminedithiol in sterile, pharmaceutically acceptable form.

- 2. An ester-substituted diaminedithiol of the formula:**



or a pharmaceutically suitable salt thereof

- wherein each of R¹-R¹² individually is selected from the group consisting of H, alkyl of 1-6 carbon atoms and -A-COOR wherein A is a straight or branched chain alkylene of 0-6 carbon atoms, n, o and p are independently 1 or 2, and R is alkyl of 1-6 carbon atoms, with the proviso that at least one of R¹-R¹² is -A-COOR,
- said ester-substituted diaminedithiol in sterile, pharmaceutically acceptable form.

- 55 3. A diaminedithiol of Claim 2 wherein R and any alkyl in R¹-R¹² is from 1-3 carbon atoms.
4. A diaminedithiol of Claim 2 wherein A is a straight chain alkylene of 0-3 carbon atoms.

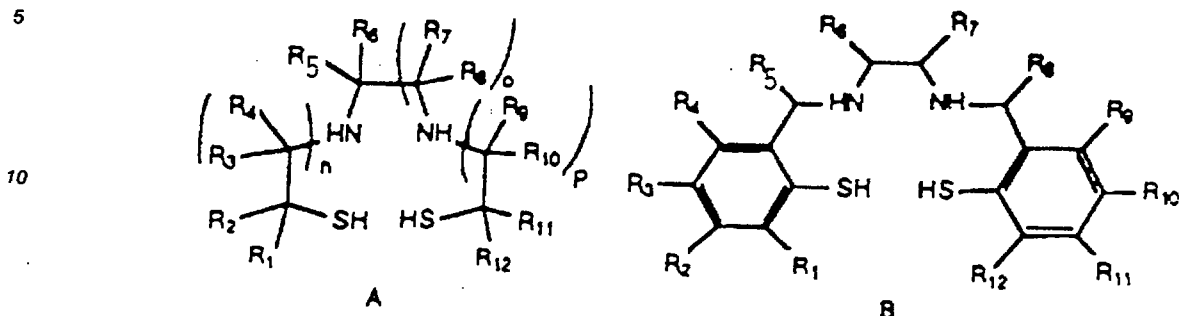


5. A diaminedithiol of Claim 2 wherein R^3 and R^{10} are $-A-COOR$ and R^4 and R^9 are H.
6. A diaminedithiol of Claim 2 wherein A is a bond and R is ethyl.
7. A diaminedithiol of Claim 2 wherein n, o and p are 1, R^3 and R^{10} are $-A-COOR$ where A is a straight chain alkylene of 0-3 carbon atoms and R is alkyl of 1-3 carbon atoms, R^4 and R^9 are H, and R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^{11} and R^{12} individually are selected from the group consisting of H, and alkyl of 1-3 carbon atoms.
8. A diaminedithiol of Claim 2 wherein 1-4 of R^1-R^{12} is $-A-COOR$.
9. A diaminedithiol of Claim 2 wherein n, o and p are 1, and 1-4 of R^1-R^{12} is $-A-COOR$.
10. A diaminedithiol of Claim 2 wherein the diaminedithiol is non-aminated, and R and any alkyl in R^1-R^{12} is from 1-3 carbon atoms.
11. A diaminedithiol of Claim 2 wherein R^3 and R^{10} are $-A-COOR$ and R^4 and R^9 are H and n, o and p are 1.
12. A diaminedithiol of Claim 2 wherein A is a bond and the stereochemistry at the position where that bond is attached to the diaminedithiol backbone is L.
13. The sterile, pharmaceutically acceptable diaminedithiol of Claim 2 which is selected from N,N'-1,2-ethylenediylbis-L-cysteine diethylester, dihydrochloride, N,N'-1,2-ethylenediylbis-L-cysteine, dimethylester, dihydrochloride, and N,N'-1,2-ethylenediylbis-L-cysteine, di-n-propylester, dihydrochloride.
14. A kit comprising a predetermined quantity of a sterile, pharmaceutically acceptable ester-substituted diaminedithiol of any one of claims 1 to 13 and a predetermined quantity of a sterile, non-pyrogenic reducing agent for reducing a preselected radionuclide.
15. A kit of Claim 14 wherein the reducing agent is a stannous salt for reducing technetium-99m.
16. A radiopharmaceutical consisting essentially of a lipophilic, charge neutral radionuclide complex of a diaminedithiol ligand according to any one of claims 1 to 13 having at least 1 ester group of the formula $-A-COOR$ where A is a straight or branched chain alkylene of 0-6 carbon atoms and R is an alkyl group of 1-6 carbon atoms.
17. A radiopharmaceutical of Claim 16 wherein the radionuclide is a radioactive isotope of Tc, Ru, Cu, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb, or Ta.
18. A radiopharmaceutical of Claim 16 wherein the radionuclide is technetium-99m.
19. A radiopharmaceutical of Claim 16 wherein the diaminedithiol is selected from the diaminedithiols of any one of claims 1 to 13.
20. A process of radioimaging comprising (i) administering parenterally to a mammal a composition of any one of claims 16 to 19 in a pharmaceutically suitable carrier, and (ii) radioimaging the brain of the mammal after allowing sufficient time for the composition to localize in the brain.
21. A process for preparing a radiopharmaceutical according to any one of claims 16 to 19 comprising admixing a diaminedithiol of any one of claims 1 to 13 and a salt of a radioactive metal in the presence of a suitable reducing agent, if required, in aqueous media at temperatures from room temperature to reflux temperature or even higher for a period from 1 minute to 2 hours.



Claims for the following Contracting States : ES, GR

1. Process for the preparation of an ester-substituted diaminedithiol of the formula:

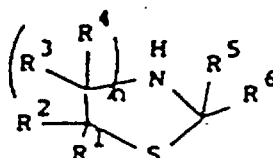


or a pharmaceutically suitable salt thereof wherein:

each of R_1 - R_{12} individually is selected from the group consisting of H, alkyl of 1-10 carbon atoms and -A-COOR wherein A is a straight or branched chain alkylene of 0-10 carbon atoms, n, o, and p are independently 1 or 2, and R is (a) alkyl of 1-10 carbon atoms, (b) phenyl or benzyl optionally substituted with up to 5 ring substituents each selected from alkyl of 1-4 carbon atoms, fluoro, chloro, bromo, nitro, alkoxy of 1-4 carbon atoms, carboxyl, or a carboxylic acid ester of 1-4 carbon atoms, or (c) a 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O or S, with the proviso that at least one of R_1 - R_{12} is -A-COOR,

said ester-substituted diaminedithiol in sterile, pharmaceutically acceptable form.

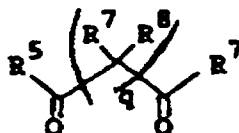
- whereby said process comprises for the preparation of A reductive dimerization in liquid ammonia of a substituted thiazolidine or a tetrahydro-1,3-thiazene of the formula



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and n are as defined above

followed by esterification with methanol or ethanol using gaseous hydrogen chloride as catalyst, or alternatively

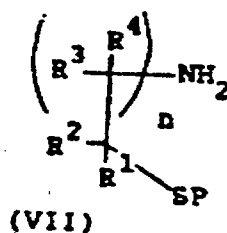
reductive amination of glyoxal or a 1,2-diketone or 1,3-diketone moiety of the formula VI



wherein q = 0 or 1,

with an aminothiols of formula VII

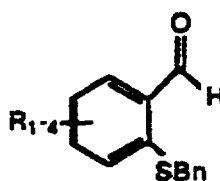




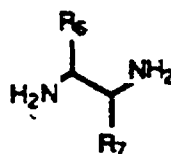
wherein P is a protecting group selected from methoxymethyl, methoxyethoxymethyl, p-methoxybenzyl or benzyl,

and which is then removed by appropriate methods,

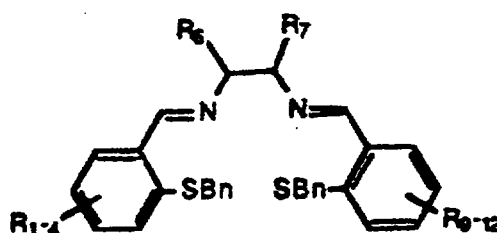
- and said process for the production of B comprises reaction of a thiol substituted benzaldehyde of the formula



with an amine of the formula



to form a diimide of the formula

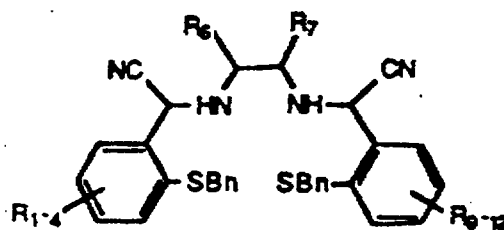


which is then reduced, deprotected and esterified
or alternatively

reaction of said thiol substituted benzaldehyde with the amine in the presence of a cyanide

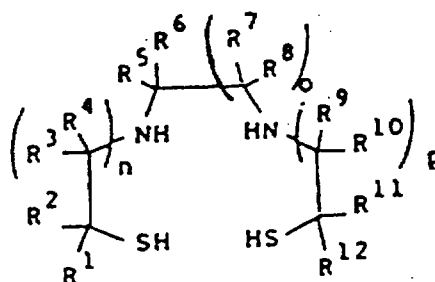


nucleophile in a Strecker-synthesis to form the bis-amino-nitrile of the formula



which is then hydrolyzed, deprotected and esterified.

2. Process according to claim 1 for the preparation of an ester-substituted diaminodithiol of the formula:



or a pharmaceutically suitable salt thereof

wherein each of R^1 - R^{12} individually is selected from the group consisting of H, alkyl of 1-6 carbon atoms and -A-COOR wherein A is a straight or branched chain alkylene of 0-6 carbon atoms, n, o and p are independently 1 or 2, and R is alkyl of 1-6 carbon atoms, with the proviso that at least one of R^1 - R^{12} is -A-COOR,

said ester-substituted diaminodithiol in sterile, pharmaceutically acceptable form.

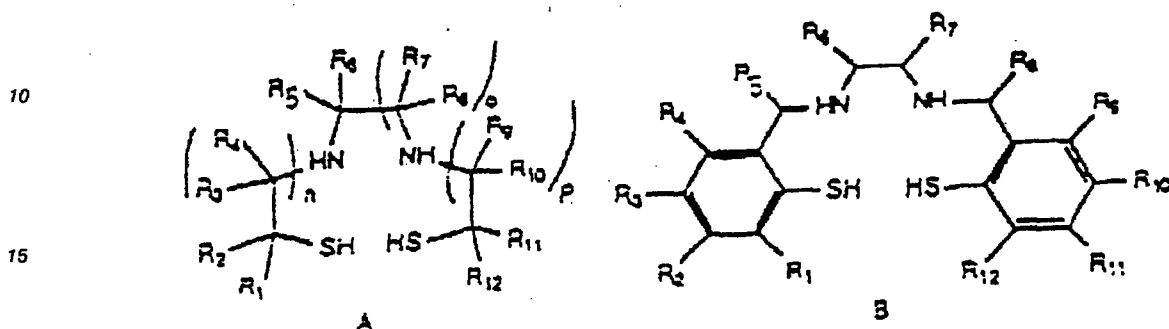
3. The process of Claim 2 wherein R and any alkyl in R^1 - R^{12} is from 1-3 carbon atoms.
4. The process of Claim 2 wherein A is a straight chain alkylene of 0-3 carbon atoms.
5. The process of Claim 2 wherein R^3 and R^{10} are -A-COOR and R^4 and R^9 are H.
6. The process of Claim 2 wherein A is a bond and R is ethyl.
7. The process of Claim 2 wherein n, o and p are 1, R^3 and R^{10} are -A-COOR where A is a straight chain alkylene of 0-3 carbon atoms and R is alkyl of 1-3 carbon atoms, R^4 and R^9 are H, and R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^{11} and R^{12} individually are selected from the group consisting of H, and alkyl of 1-3 carbon atoms.
8. The process of Claim 2 wherein 1-4 of R^1 - R^{12} is -A-COOR.
9. The process of Claim 2 wherein n, o and p are 1, and 1-4 of R^1 - R^{12} is -A-COOR.
10. The process of Claim 2 wherein the diaminodithiol is non-aminated, and R and any alkyl in R^1 - R^{12} is from 1-3 carbon atoms.
11. The process of Claim 2 wherein R^3 and R^{10} are -A-COOR and R^4 and R^9 are H and n, o and p are 1.
12. The process of Claim 2 wherein A is a bond and the stereochemistry at the position where that bond is attached to the diaminodithiol backbone is L.



Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

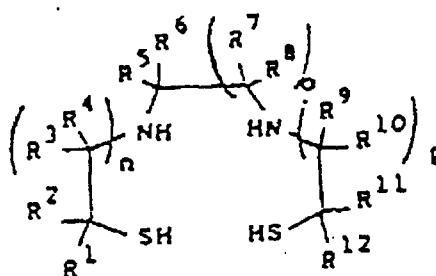
1. Un diaminodithiol substitué par des groupes esters représenté par les formules;



ou l'un de ses sels acceptables d'un point de vue pharmaceutique, dans lesquelles:

chaque R^1 à R^{12} est choisi individuellement dans le groupe comprenant un atome d'hydrogène, un groupe alkyle ayant de 1 à 10 atomes de carbone et -A-COOR dans lequel A est un groupe alkylène à chaîne droite ou ramifiée ayant de 0 à 10 atomes de carbone, n, o et p sont de façon indépendante 1 ou 2, et R est (a) un groupe alkyle ayant de 1 à 10 atomes de carbone, (b) un groupe phényle ou benzyle dont le cycle est éventuellement substitué avec un maximum de 5 substituants choisis chacun parmi un groupe alkyle ayant de 1 à 4 atomes de carbone, un atome de fluor chlore brome, un groupe nitro, alcoxy ayant de 1 à 4 atomes de carbone, carboxy ou un ester d'acide carboxylique ayant de 1 à 4 atomes de carbone, ou (c) un noyau hétérocyclique à 5 ou 6 chaînons comportant 1 ou 2 hétéroatomes choisis parmi N, O ou S, à condition qu'au moins l'un des R^1 à R^{12} soit -A-COOR, ce diaminodithiol substitué par des groupes esters étant sous une forme stérile acceptable d'un point de vue pharmaceutique.

2. Un diaminodithiol substitué par des groupes esters de formule;



ou un sel de celui-ci acceptable du point de vue pharmaceutique,

dans laquelle chaque R^1 à R^{12} est choisi individuellement dans le groupe comprenant un atome d'hydrogène, un groupe alkyle ayant de 1 à 5 atomes de carbone et -A-COOR dans lequel A est un groupe alkylène à chaîne droite ou ramifiée ayant de 0 à 6 atomes de carbone, n, o et p sont de façon indépendante 1 ou 2 et R est un groupe alkyle ayant de 1 à 6 atomes de carbone, à condition qu'au moins l'un des groupes R^1 à R^{12} soit -A-COOR

ce diaminodithiol substitué par des groupes esters étant sous une forme stérile acceptable d'un point de vue pharmaceutique.

3. Un diaminodithiol selon la revendication 2, dans lequel R et un quelconque groupe alkyle de R^1 à R^{12} comprend de 1 à 3 atomes de carbone.



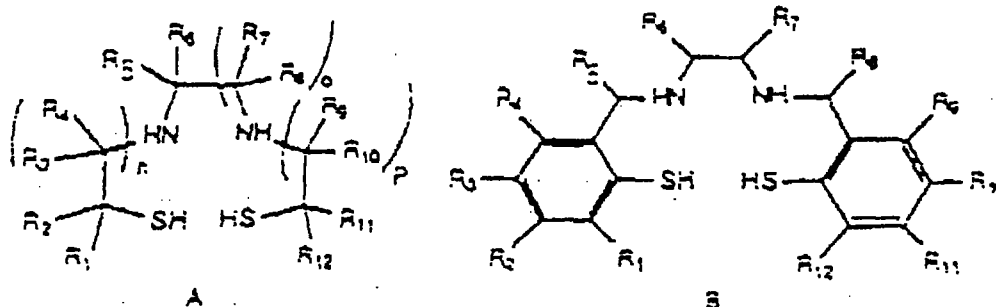
4. Un diaminodithiol selon la revendication 2, dans lequel A est un groupe alkylène à chaîne droite ayant de 0 à 3 atomes de carbone.
- 5 5. Un diaminodithiol selon la revendication 2, dans lequel R³ et R¹⁰ sont un radical -A-COOR et R⁴ et R⁹ sont des atomes d'hydrogène.
6. Un diaminodithiol selon la revendication 2, dans lequel A est une liaison et R un groupe éthyle.
- 10 7. Un diaminodithiol selon la revendication 2, dans lequel n, o et p sont 1, R³ et R¹⁰ sont -A-COOR dans lequel A est un groupe alkylène à chaîne droite ayant de 0 à 3 atomes de carbone et R est un groupe alkyle ayant de 1 à 3 atomes de carbone, R⁴ et R⁹ sont des atomes d'hydrogène et R¹, R², R⁵, R⁶, R⁷, R⁸, R¹¹ et R¹² sont individuellement choisis dans le groupe consistant en un atome d'hydrogène et un groupe alkyle ayant de 1 à 3 atomes de carbone.
- 15 8. Un diaminodithiol selon la revendication 2, dans lequel 1 à 4 des groupes R¹ à R¹² sont un radical -A-COOR.
9. Un diaminodithiol selon la revendication 2, dans lequel n, o et p sont 1, et 1 à 4 des groupes R¹ à R¹² sont on radical -A-COOR.
- 20 10. Un diaminodithiol selon la revendication 2, dans lequel le diaminodithiol n'est pas aminé, et R et un quelconque groupe alkyle dans R¹ à R¹² comprend de 1 à 3 atomes de carbone.
11. Un diaminodithiol selon la revendication 2, dans lequel R³ et R¹⁰ sont un radical -A-COOR, R⁴ et R⁹ sont des atomes d'hydrogène et n, o et p sont 1.
- 25 12. Un diaminodithiol selon la revendication 2, dans lequel A est une liaison et la stéréochimie à la position à laquelle cette liaison est attachée au squelette du diaminodithiol est L.
- 30 13. Le diaminodithiol stérile, acceptable d'un point de vue pharmaceutique selon la revendication 2, qui est choisi dans le groupe consistant en dichlorhydrate de l'ester diéthylique de N,N'-1,2-éthylènediylbis-L-cystéine, dichlorhydrate de l'ester diméthylique de N,N'-1,2-éthylènediylbis-L-cystéine, dichlorhydrate de l'ester di-n-propylique de N,N'-1,2-éthylènediylbis-L-cystéine.
- 35 14. Une trousse comprenant une quantité prédéterminée d'un diaminodithiol substitué par des esters, stérile, acceptable d'un point de vue pharmaceutique selon l'une quelconque des revendications 1 à 13, et une quantité prédéterminée d'un agent réducteur, stérile, non pyrogène, pour réduire un radionucléide choisi à l'avance.
- 40 15. Une trousse selon la revendication 14, dans laquelle l'agent réducteur est un sel stanneux pour réduire le technétium-99m.
16. Un produit pharmaceutique radioactif comprenant essentiellement un complexe lipophile de charge neutre de radionucléide et d'un ligand de type diaminodithiol selon l'une quelconque des revendications 1 à 13 ayant au moins un groupe ester de formule -A-COOR dans lequel A est on groupe alkylène à chaîne droite ou ramifiée ayant de 0 à 6 atomes de carbone et R est un groupe alkyle ayant de 1 à 6 atomes de carbone.
- 45 17. Un produit pharmaceutique radioactif selon la revendication 16 dans lequel le radionucléide est un isotope radioactif de Tc, Ru, Cu, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb ou Ta.
- 50 18. Un produit pharmaceutique radioactif selon la revendication 16, dans lequel le radionucléide est le technétium-99m.
- 55 19. Un produit pharmaceutique radioactif selon la revendication 16, dans lequel la diaminodithiol est choisi parmi les diaminodithiols suivant l'une quelconque des revendications 1 à 13.



20. Un procédé d'imagerie radioactive comprenant (i) l'administration par voie parentérale à un mammifère d'une composition selon l'une quelconque des revendications 16 à 19 dans un support convenable d'un point de vue pharmaceutique et (ii) l'imagerie radioactive du cerveau du mammifère après avoir laissée, suffisamment de temps pour que la composition se localise dans le cerveau.
21. Un procédé pour la préparation d'un produit pharmaceutique radioactif selon l'une quelconque des revendications 16 à 19, comprenant le mélange d'un diaminodithiol selon l'une quelconque des revendications 1 à 13 et d'un sel de métal radioactif en présence d'un agent réducteur convenable, si cela est nécessaire, dans un milieu aqueux à des températures comprises entre la température ambiante et la température de reflux ou même supérieures pendant une durée de 1 minute à deux heures.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un diaminodithiol substitué par des esters représenté par les formules;



ou de l'un de ses sels acceptables d'un point de vue pharmaceutique, dans lesquelles;

chaque R^1 à R^{12} est choisi individuellement dans le groupe comprenant un atome d'hydrogène, un groupe alkyle ayant de 1 à 10 atomes de carbone et -A-COOR dans lequel A est un groupe alkylène à chaîne droite ou ramifiée ayant de 0 à 10 atomes de carbone, n, o et p sont de façon indépendante 1 ou 2, et R est (a) un groupe alkyle ayant de 1 à 10 atomes de carbone, (b) un groupe phényle ou benzyle dont le cycle est éventuellement substitué avec un maximum de 5 substituants choisis chacun parmi un groupe alkyle ayant de 1 à 4 atomes de carbone, un atome de fluor chlore, brome, un groupe nitro, alcoxy ayant de 1 à 4 atomes de carbone, carboxy ou on ester d'acide carboxylique ayant de 1 à 4 atomes de carbone, ou (c) un noyau hétérocyclique à 5 ou 6 chaînons comportant 1 ou 2 hétéroatomes choisis parmi N, O ou S, à condition qu'au moins l'un des R^1 à R^{12} soit -A-COOR, ce diaminodithiol substitué par des groupes esters étant sous une forme stérile acceptable d'un point de vue pharmaceutique,

- ce procédé comprenant pour la préparation de A :

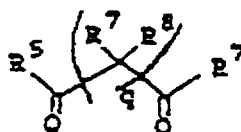
la dimérisation réductrice dans l'ammoniac liquide d'une thiazolidine substituée ou d'un tétrahydro-1,3-thiazène de formule



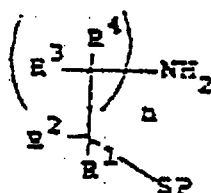
dans laquelle R^1 , R^2 , R^3 , R^4 , R^5 , R^6 et n sont tels que définis plus haut, puis l'estérification par du méthanol ou de l'éthanol avec du chlorure d'hydrogène gazeux comme catalyseur, ou, dans une variante,



l'amination réductrice du glyoxal ou d'une partie 1,2-dicétone ou 1,3-dicétone de formule VI

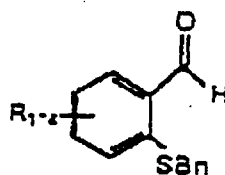


dans laquelle $q = 0$ ou 1 ,
avec un aminothiols de formule VII

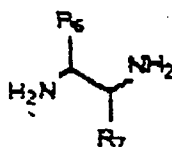


VII

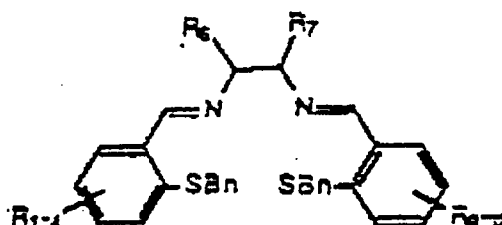
dans laquelle P est un groupe protecteur choisi parmi les groupes méthoxyméthyle, méthoxyéthoxyméthyle, p-méthoxybenzyle ou benzyle,
et qui est ensuite éliminé par des procédés appropriés,
et ce procédé comprenant pour la production de B:
la réaction d'un benzaldéhyde à substituant thiol de formule



avec une amine de formule



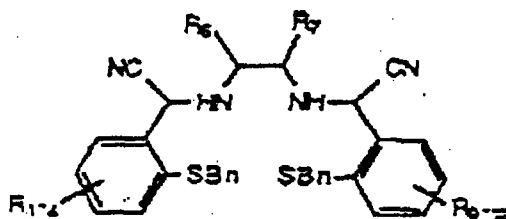
pour former un diimide de formula



lequel est ensuite réduit, déprotégé et estérifié, ou dans une variante,
la réaction de ce benzaldéhyde à substituant thiol avec l'amine en présence d'un nucléophile de

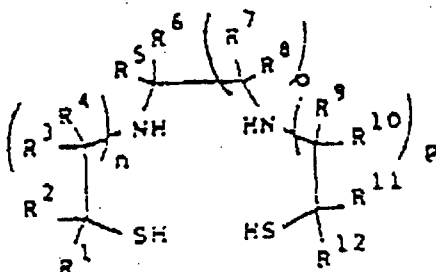


type cyanure dans une synthèse de Strecker pour former le bis-amino-nitrile de formule



qui est ensuite hydrolysé, déprotégé et estérifié,

2. Procédé selon la revendication 1 pour la préparation d'un diaminodithiol substitué par des groupes esters ayant pour formule;



ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle chaque R^1 à R^{12} est choisi individuellement dans le groupe comprenant un atome d'hydrogène, un groupe alkyle ayant de 1 à 6 atomes de carbone et $-A-COOR$ dans lequel A est un groupe alkylène à chaîne droite ou ramifiée ayant de 0 à 6 atomes de carbone, n , o et p sont de façon indépendante 1 ou 2, et R est un groupe alkyle ayant de 1 à 6 atomes de carbone, à condition qu'au moins l'un des groupes R^1 à R^{12} soit $-A-COOR$,

ce diaminodithiol substitué par des esters étant sous une forme stérile acceptable d'un point de vue pharmaceutique.

3. Procédé selon la revendication 2, dans lequel R et un quelconque groupe alkyle dans R^1 à R^{12} comprend de 1 à 3 atomes de carbone,
4. Procédé selon la revendication 2, dans lequel A est un groupe alkylène à chaîne droite ayant de 0 à 3 atomes de carbone.
5. Procédé selon la revendication 2, dans lequel R^3 et R^{10} sont un radical $-A-COOR$ et R^4 et R^9 sont des atomes d'hydrogène.
6. Procédé selon la revendication 2, dans lequel A est une liaison et R un groupe éthyle.
7. Procédé selon la revendication 2, dans lequel n , o et p sont 1, R^3 et R^{10} sont un radical $-A-COOR$ dans lequel A est un groupe alkylène à chaîne droite ayant de 0 à 3 atomes de carbone et R est un groupe alkyle ayant de 1 à 3 atomes de carbone, R^4 et R^9 sont des atomes d'hydrogène, et R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^{11} et R^{12} sont individuellement choisis dans le groupe consistant en un atome d'hydrogène et un groupe alkyle ayant de 1 à 3 atomes de carbone.
8. Procédé selon la revendication 2, dans lequel 1 à 4 des groupes R^1 à R^{12} sont un radical $-A-COOR$.
9. Procédé selon la revendication 2, dans lequel n , o et p sont 1 et 1 à 4 des groupes R^1 à R^{12} sont un radical $-A-COOR$.



10. Procédé selon la revendication 2, dans lequel le diaminodithiol n'est pas aminé et R et un quelconque groupe alkyle dans R^{11} à R^{12} comprend de 1 à 3 atomes de carbone.
11. Procédé selon la revendication 2, dans lequel R^3 et R^{10} sont un radical $-A-COOR$, R^4 et R^9 sont des atomes d'hydrogène et n, o et p sont 1.
12. Procédé selon la revendication 2, dans lequel A est une liaison et la stéréochimie à la position à laquelle cette liaison est attachée au squelette du diaminodithiol est L.

Patentansprüche

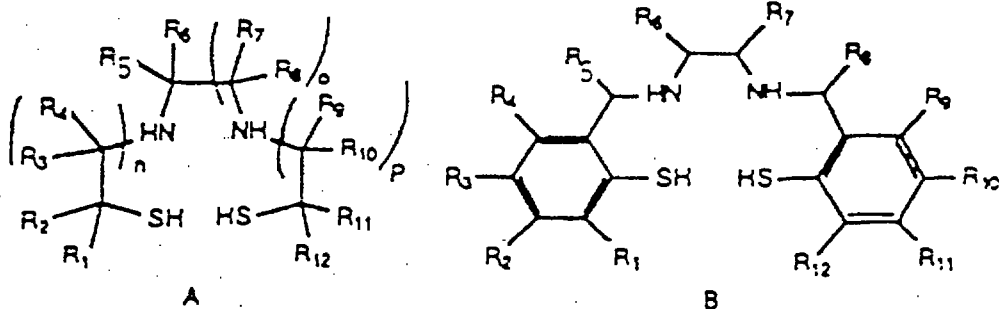
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Ester-substituiertes Diamindithiol der Formel

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oder ein pharmazeutisch geeignetes Salz desselben, worin

R_1 bis R_{12} jeweils einzeln aus der aus H, Alkyl mit 1 bis 10 Kohlenstoff-Atomen und $-A-COOR$, worin A ein geradkettiges oder kettenverzweigtes Alkyl mit 0 bis 10 Kohlenstoff-Atomen ist, bestehenden Gruppe ausgewählt sind,

n, o und p unabhängig voneinander 1 oder 2 sind und

R

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(a) Alkyl mit 1 bis 10 Kohlenstoff-Atomen,

(b) Phenyl oder Benzyl, das gegebenenfalls mit bis zu 5 Ring-Substituenten substituiert ist, die jeweils aus Alkyl mit 1 bis 4 Kohlenstoff-Atomen, Fluor, Chlor, Brom, Nitro, Alkoxy mit 1 bis 4 Kohlenstoff-Atomen, Carboxyl oder einem Carbonsäureester mit 1 bis 4 Kohlenstoff-Atomen ausgewählt sind, oder

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(c) ein fünf- oder sechsgliedriger heterocyclischer Ring ist, der 1 oder 2 aus N, O oder S ausgewählte Hetero-Atome enthält,

mit der Maßgabe, daß wenigstens einer der Substituenten R_1 bis R_{12} $-A-COOR$ ist,

wobei das ester-substituierte Diamindithiol in steriler, pharmazeutisch annehmbarer Form vorliegt.

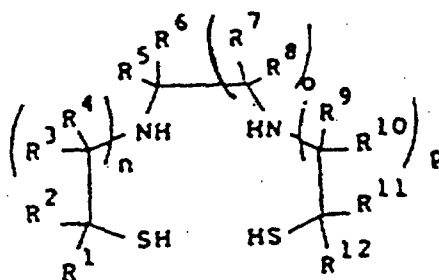
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2. Ester-substituiertes Diamindithiol der Formel



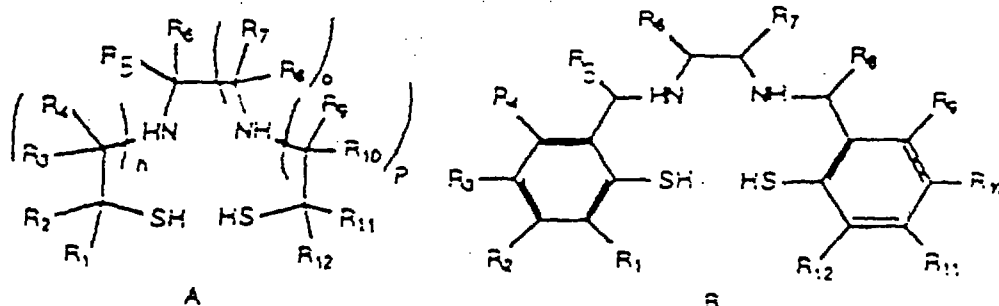
- oder ein pharmazeutisch geeignetes Salz desselben, worin
 R^1 bis R^{12} jeweils einzeln aus der aus H, Alkyl mit 1 bis 6 Kohlenstoff-Atomen und -A-COOR, worin A
 ein geradkettiges oder kettenverzweigtes Alkyl mit 0 bis 6 Kohlenstoff-Atomen ist, bestehenden
 Gruppe ausgewählt sind,
 n , o und p unabhängig voneinander 1 oder 2 sind und
 R Alkyl mit 1 bis 6 Kohlenstoff-Atomen ist,
 mit der Maßgabe, daß wenigstens einer der Substituenten R^1 bis R^{12} -A-COOR ist,
 wobei das ester-substituierte Diamindithiol in steriler, pharmazeutisch annehmbarer Form vorliegt.
3. Diamindithiol nach Anspruch 2, worin R und etwaiges Alkyl in R^1 bis R^{12} 1 bis 3 Kohlenstoff-Atome
 aufweist.
4. Diamindithiol nach Anspruch 2, worin A ein geradkettiges Alkyl mit 0 bis 3 Kohlenstoff-Atomen ist.
5. Diamindithiol nach Anspruch 2, worin R^3 und R^{10} -A-COOR sind und R^4 und R^9 H sind.
6. Diamindithiol nach Anspruch 2, worin A eine Bindung ist und R Ethyl ist.
7. Diamindithiol nach Anspruch 2, worin
 n , o und p 1 sind,
 R^3 und R^{10} -A-COOR sind, worin A ein geradkettiges Alkyl mit 0 bis 3 Kohlenstoff-Atomen ist und R
 Alkyl mit 1 bis 3 Kohlenstoff-Atomen ist,
 R^4 und R^9 H sind und
 R^1 R^2 R^5 R^6 R^7 R^8 R^{11} und R^{12} einzeln aus der aus H und Alkyl mit 1 bis 3 Kohlenstoff-Atomen
 bestehenden Gruppe ausgewählt sind.
8. Diamindithiol nach Anspruch 2, worin einer bis vier der Substituenten R^1 bis R^{12} -A-COOR ist/sind.
9. Diamindithiol nach Anspruch 2, worin n , o und p 1 sind und einer bis vier der Substituenten R^1 bis R^{12}
 -A-COOR ist/sind.
10. Diamindithiol nach Anspruch 2, worin das Diamindithiol nicht-aminiert ist und R und etwaiges Alkyl in
 R^1 bis R^{12} 1 bis 3 Kohlenstoff-Atome aufweist.
11. Diamindithiol nach Anspruch 2, worin R^3 und R^{10} -A-COOR sind und R^4 und R^9 H sind und n , o und p
 1 sind.
12. Diamindithiol nach Anspruch 2, worin A eine Bindung ist und die Stereochemie in der Position, in der
 diese Bindung mit dem Diamindithiol-Gerüst verknüpft ist, L ist.
13. Steriles, pharmazeutisch annehmbares Diamindithiol nach Anspruch 2, das ausgewählt ist aus
 N,N' -1,2-Ethylendiyl-bis-L-cystein-diethylester-dihydrochlorid,
 N,N' -1,2-Ethylendiyl-bis-L-cystein-dimethylester-dihydrochlorid und
 N,N' -1,2-Ethylendiyl-bis-L-cystein-di-n-propylester-dihydrochlorid.



14. Kit, umfassend eine vorher festgelegte Menge eines sterilen, pharmazeutisch annehmbaren, ester-substituierten Diamindithiols nach irgendeinem der Ansprüche 1 bis 13 und eine vorher festgelegte Menge eines sterilen, nicht-pyrogenen Reduktionsmittels zum Reduzieren eines vorher ausgewählten Radionuklids.
15. Kit nach Anspruch 14, worin das Reduktionsmittel ein Zinn(II)-Salz zum Reduzieren von Technetium-99m ist.
16. Radiopharmazeutikum, bestehend im wesentlichen aus einem lipophilen, ladungsneutralen Radionuklid-Komplex eines Diamindithiol-Liganden nach irgendeinem der Ansprüche 1 bis 13 mit wenigstens einer Ester-Gruppe der Formel $-A-COOR$, worin A ein geradkettiges oder kettenverzweigtes Alkyl mit 0 bis 6 Kohlenstoff-Atomen ist und R eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoff-Atomen ist.
17. Radiopharmazeutikum nach Anspruch 16, worin das Radionuklid ein radioaktives Isotop von Tc, Ru, Cu, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb oder Ta ist.
18. Radiopharmazeutikum nach Anspruch 16, worin das Radionuklid Technetium-99m ist.
19. Radiopharmazeutikum nach Anspruch 16, worin das Diamindithiol aus den Diamindithiolen nach irgendeinem der Ansprüche 1 bis 13 ausgewählt ist.
20. Verfahren zur radiographischen Abbildung, umfassend
 (i) die parenterale Verabreichung einer Zusammensetzung nach irgendeinem der Ansprüche 16 bis 19 in einem pharmazeutisch geeigneten Träger an einen Säuger und
 (ii) die radiographische Abbildung des Gehirns des Säugers nach Verstreichenlassen einer hinreichenden Zeit, damit sich die Zusammensetzung in dem Gehirn lokalisieren kann.
21. Verfahren zur Herstellung eines Radiopharmazeutikums nach irgendeinem der Ansprüche 16 bis 19, umfassend das Vermischen eines Diamindithiols nach irgendeinem der Ansprüche 1 bis 13 und eines Salzes eines radioaktiven Metalls in Gegenwart eines geeigneten Reduktionsmittels, erforderlichenfalls in wäßrigem Medium, bei Temperaturen von Raumtemperatur bis zur Rückfluß-Temperatur oder noch darüber während eines Zeitraums von 1 min bis 2 h.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines ester-substituierten Diamindithiols der Formel



oder eines pharmazeutisch geeigneten Salzes desselben, worin

R₁ bis R₁₂ jeweils einzeln aus der aus H, Alkyl mit 1 bis 10 Kohlenstoff-Atomen und $-A-COOR$, worin A ein geradkettiges oder kettenverzweigtes Alkyl mit 0 bis 10 Kohlenstoff-Atomen ist, bestehenden Gruppe ausgewählt sind,

n, o und p unabhängig voneinander 1 oder 2 sind und

R

(a) Alkyl mit 1 bis 10 Kohlenstoff-Atomen,



(b) Phenyl oder Benzyl, das gegebenenfalls mit bis zu 5 Ring-Substituenten substituiert ist, die jeweils aus Alkyl mit 1 bis 4 Kohlenstoff-Atomen, Fluor, Chlor, Brom, Nitro, Alkoxy mit 1 bis 4 Kohlenstoff-Atomen, Carboxyl oder einem Carbonsäureester mit 1 bis 4 Kohlenstoff-Atomen ausgewählt sind, oder

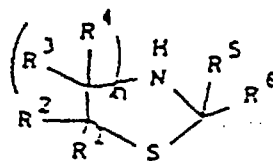
5 (c) ein fünf- oder sechsgliedriger heterocyclischer Ring ist, der 1 oder 2 aus N, O oder S ausgewählte Hetero-Atome enthält,

mit der Maßgabe, daß wenigstens einer der Substituenten R_1 bis R_{12} -A-COOR ist,

wobei das ester-substituierte Diamindithiol in steriler, pharmazeutisch annehmbarer Form vorliegt,

wobei das Verfahren für die Herstellung von A

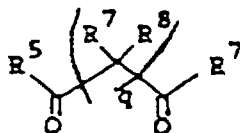
10 die reduzierende Dimerisierung eines substituierten Thiazolidins oder eines Tetrahydro-1,3-thiazens der Formel



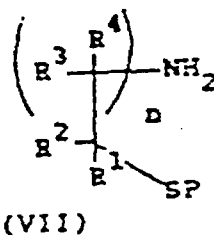
in flüssigem Ammoniak, wobei

25 R^1 R^2 R^3 R^4 , R^5 , R^6 und n die oben angegebenen Bedeutungen haben, und danach die Veresterung mit Methanol oder Ethanol unter Verwendung von gasförmigem Hydrogenchlorid als Katalysator oder alternativ

die reduzierende Aminierung von Glyoxal oder einer 1,2-Diketon- oder 1,3-Diketon-Struktureinheit der Formel VI



40 worin $q = 0$ oder 1 , mit einem Aminothiol der Formel VII

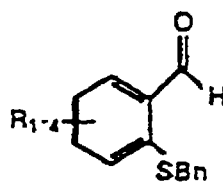


50 worin P eine Schutzgruppe ist, die aus Methoxymethyl, Methoxyethoxymethyl, p-Methoxybenzyl, Benzyl ausgewählt ist und die danach mittels geeigneter Methoden entfernt wird, umfaßt und

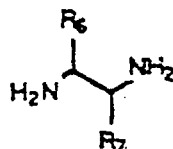
55 wobei das Verfahren für die Herstellung von B

die Umsetzung eines thiol-substituierten Benzaldehyds der Formel

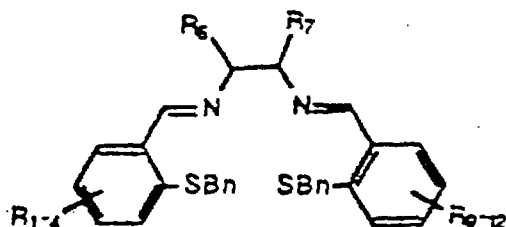




mit einem Amin der Formel

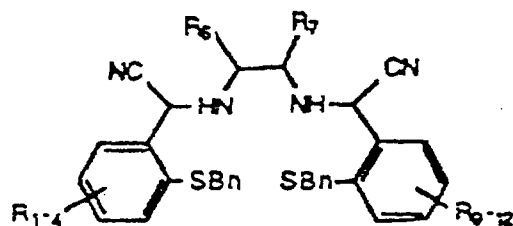


unter Bildung eines Diimids der Formel



das dann reduziert, von der Schutzgruppe befreit und verestert wird, oder alternativ

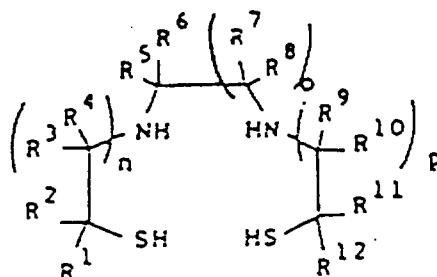
die Umsetzung des genannten thiol-substituierten Benzaldehyds mit dem Amin in Gegenwart eines Cyanid-Nucleophils in einer Strecker-Synthese unter Bildung des Bis-aminonitrils der Formel



das dann reduziert, von der Schutzgruppe befreit und verestert wird, umfaßt.



2. Verfahren nach Anspruch 1 zur Herstellung eines estersubstituierten Diamindithiols der Formel



- oder eines pharmazeutisch geeigneten Salzes desselben, worin
 R^1 bis R^{12} jeweils einzeln aus der aus H, Alkyl mit 1 bis 6 Kohlenstoff-Atomen und -A-COOR, worin A ein geradkettiges oder kettenverzweigtes Alkyl mit 0 bis 6 Kohlenstoff-Atomen ist, bestehenden Gruppe ausgewählt sind,
 n , o und p unabhängig voneinander 1 oder 2 sind und
 R Alkyl mit 1 bis 6 Kohlenstoff-Atomen ist,
mit der Maßgabe, daß wenigstens einer der Substituenten R^1 bis R^{12} -A-COOR ist, wobei das ester-substituierte Diamindithiol in steriler, pharmazeutisch annehmbarer Form vorliegt.
3. Verfahren nach Anspruch 2, worin R und etwaiges Alkyl in R^1 bis R^{12} 1 bis 3 Kohlenstoff-Atome aufweist.
4. Verfahren nach Anspruch 2, worin A ein geradkettiges Alkyl mit 0 bis 3 Kohlenstoff-Atomen ist.
5. Verfahren nach Anspruch 2, worin R^3 und R^{10} -A-COOR sind und R^4 und R^9 H sind.
6. Verfahren nach Anspruch 2, worin A eine Bindung ist und R Ethyl ist.
7. Verfahren nach Anspruch 2, worin
 n , o und p 1 sind,
 R^3 und R^{10} -A-COOR sind, worin A ein geradkettiges Alkyl mit 0 bis 3 Kohlenstoff-Atomen ist und R Alkyl mit 1 bis 3 Kohlenstoff-Atomen ist,
 R^4 und R^9 H sind und
 R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^{11} und R^{12} einzeln aus der aus H und Alkyl mit 1 bis 3 Kohlenstoff-Atomen bestehenden Gruppe ausgewählt sind.
8. Verfahren nach Anspruch 2, worin einer bis vier der Substituenten R^1 bis R^{12} -A-COOR ist/sind.
9. Verfahren nach Anspruch 2, worin n , o und p 1 sind und einer bis vier der Substituenten R^1 bis R^{12} -A-COOR ist/sind.
10. Verfahren nach Anspruch 2, worin das Diamindithiol nicht-aminiert ist und R und etwaiges Alkyl in R^1 bis R^{12} 1 bis 3 Kohlenstoff-Atome aufweist.
11. Verfahren nach Anspruch 2, worin R^3 und R^{10} -A-COOR sind und R^4 und R^9 H sind und n , o und p 1 sind.
12. Verfahren nach Anspruch 2, worin A eine Bindung ist und die Stereochemie in der Position, in der diese Bindung mit dem Diamindithiol-Gerüst verknüpft ist, L ist.

