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N,N',N'',N'''-Tetraalkylcyclam Derivatives: Synthesis, ^{99m}Tc-Labelling, and Biological Properties

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SUMMARY

We synthesized *N,N',N'',N'''*-tetraalkylcyclam derivatives in which alkyl groups were ethyl, propyl, butyl, methoxyethyl, and ethoxyethyl. We attempted to label the compounds with ^{99m}Tc. The cyclams with methyl, ethyl, and propyl could be labelled. The labelled *N,N',N'',N'''*-tetraalkylcyclam derivatives showed +1 charge. They excreted rapidly through the kidney in mice. The liver-uptake increased slightly as the lipophilicity increased. However, the myocardial uptake was low unlikely with the +1 charged myocardial imaging agents.
KEY WORDS: cyclam, ^{99m}Tc, tetraalkylcyclam, tetraazacyclotetradecane

INTRODUCTION

Polyamines have been known as excellent chelating agents for various kinds of metals, such as Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, and Hg^{2+} (1). Similarly, reaction of ^{99m}Tc-pertechnetate with ethylenediamine in the presence of Sn(II) appears to give a single cationic species which is very stable in weak alkaline medium (2). Cyclam (1,4,8,11-tetraazacyclotetradecane), a kind of polyamine, was also reported to form a positively charged stable chelate with ^{99m}Tc (3). A tetraacetate derivative of cyclam (1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid, TETA) has been used as a bichelating agent for labelling biological materials with radioisotopes of copper (4). A variety of cyclam derivatives also have been synthesized for the labelling of proteins with technetium or rhenium (5, 6). Technetium atom in the chelate of cyclam or ethylenediamine has been proved to form a $Tc(V)O_2$ core by X-ray crystallography and NMR spectroscopy (7, 8). Cyclam and tetraamine form more stable ^{99m}Tc complex than ethylenediamine due to the "macrocyclic effect" and the "chelate effect" (9).

A typical application of +1 charged ^{99m}Tc-labelled agents is myocardial imaging. The examples are isonitriles, diphosphino compounds, and Schiff's base ligands. Although, the

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charges of ^{99m}Tc itself in ^{99m}Tc-labelled isonitrile, diphosphino compounds, and Schiff's base ligands are +1, +3, and +5, respectively, the net charges are all +1. With this fact, we can guess that the net +1 charge is a major factor for myocardial uptake. Another important property of the myocardial agents is the lipophilicity. It has been reported that the agents pass cell membranes by passive diffusion due to the lipophilicity, and then bind to mitochondrial membrane due to the charge interaction (10).

Cyclam has been reported to form +1 charged chelate with ^{99m}Tc. However, it was not taken up to the myocardium but excreted rapidly through the kidney due to high hydrophilicity (3, 11). There has been an attempt to synthesize lipophilic ^{99m}Tc complexes of cyclam derivatives (12). Several monoalkylcyclam derivatives and dimethyldiphenylcyclam were synthesized to form stable single component cationic chelates with ^{99m}Tc. Although, the compounds were as lipophilic as commercialised myocardial imaging agents, none of them showed high myocardial uptake. The major difference with the commercialised agents in chemical structure was symmetricity. The reported cyclam derivatives were not symmetrical while the commercialised agents were. We tried to synthesize lipophilic and symmetrical cyclam derivatives by introducing 4 alkyl groups at the nitrogens (Fig. 1) and tested their radiochemical and biological properties.

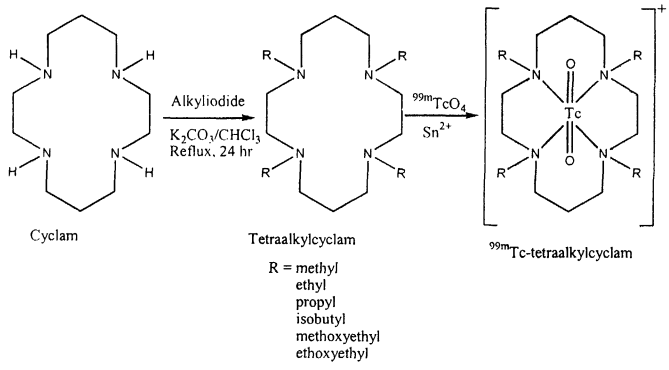

Fig.1. Synthesis of tetraalkylcyclam derivatives.

EXPERIMENTAL

General

^{1}H NMR spectroscopy was performed using a Gemini 300 model from the Varian Company (U.S.A.). Mass spectra were obtained with a Hewlett Packard Model 5973 Spectrometer (U.S.A). A gamma counter (Packard, Canberra Co., U.S.A.) and a dose calibrator (Atomlab 100, Medical Systems Inc., U.S.A.) were used for measuring low and high radioactivity, respectively. A Bio-Scan System 2000 imaging scanner was used for Radio-TLC scan. For TLC, the aluminum backed silica gel 60 F_{254} was purchased from the E.

Merck Company (Germany). Cyclam and *N,N',N'',N'''*-tetramethylcyclam (TMC) were purchased from Aldrich Company (U.S.A.). All other reagents and solvents, if not specified, were purchased from Aldrich, Fluka or Sigma (Korea) and were used without further purification

Synthesis

1,4,8,11-TETRAETHYL-1,4,8,11-TETRAAZACYCLOTETRADECANE (TEC). Cyclam (0.2 g, 0.99 mmol) was dissolved in chloroform (10 mL) containing finely ground, anhydrous K_2CO_3 (1.38 g, 9.9 mmol) and the mixture was stirred for 2 h at room temperature. A solution iodoethane (1.25 g, 7.9 mmol) in chloroform (10 mL) was added dropwise over a period of 1 h, and the mixture was refluxed for 24 h. The reaction progress was monitored by TLC. After 24 h, the chloroform was removed under reduced pressure and the product was dissolved with diethylether. Following evaporation of the diethylether under reduced pressure, the oil product was dissolved in water at pH 2 and washed with diethylether. The aqueous layer was adjusted to pH 12 and the product extracted into diethylether, dried over anhydrous sodium sulfate and evaporated. The product was thick oil (0.25g, yield 89%). The free base was treated with HCl in 1,4-dioxane and obtained as a white solid. The solid was collected by filtration and dried under vacuum. ^{1}H NMR (300 MHz, D_2O) δ 1.36 (t, 12H, -CH_2CH_3) 2.15 (q, 4H, -CH_2CH_3) 3.42 (q, 8H, -NCH_2CH_3) 3.47 (t, 8H, -$NCH_2CH_2CH_2$N-) 3.76 (s, 8H, -NCH_2CH_2N-). MS, EI (70 eV), m/z (% relative to base peak) M^+ = 312 (2), 283 (0), 267 (0), 254 (0), 226 (0), 214 (0), 202 (1), 182 (3), 169 (7), 155 (6), 141 (14), 127 (4), 111 (4), 98 (4), 84 (29), 72 (100), 56 (12).

1,4,8,11-TETRAPROPYL-1,4,8,11-TETRAAZACYCLOTETRADECANE (TPC). A solution of cyclam (0.2 g, 0.99 mmol) and K_2CO_3 (1.38 g, 9.9 mmol) in chloroform (10 mL) was treated with a solution of iodopropane (1.35 g, 7.98 mmol) in chloroform (10 mL). The product was obtained as thick oil (0.30 g, yield 83%). White powder form of HCl salt was obtained following above procedure to obtain TEC. ^{1}H NMR (300 MHz, D_2O) δ 0.96 (t, 12H, -$CH_2CH_2CH_3$) 1.78 (s, 8H, -$CH_2CH_2CH_3$) 2.13 (q, 4H, -$NCH_2CH_2CH_2$N-) 3.27 (t, 8H, -$NCH_2CH_2CH_2$N-) 3.42 (t, 8H, -$NCH_2CH_2CH_3$) 3.76 (s, 8H, -NCH_2CH_2N-). MS, EI (70 eV), m/z (% relative to base peak) M^+ = 368 (3), 353 (0), 339 (0), 325 (0), 295 (0), 282 (0), 268 (0), 256 (0), 244 (1), 223 (0), 210 (2), 197 (9), 183 (6), 171 (18), 155 (10), 141 (2), 125 (4), 112 (13), 98 (23), 86 (100), 70 (18), 58 (11).

1,4,8,11-TETRAISOBUTYL-1,4,8,11-TETRAAZACYCLOTETRADECANE (TBC). A solution of cyclam (0.2 g, 0.99 mmol) and K_2CO_3 (1.38 g, 9.9 mmol) in chloroform (10 mL) was treated with a solution of isobutyliodide (1.5 g, 7.98 mmol) in chloroform (10 mL). The product was obtained as thick oil (0.37 g, yield 88%). White powder form of HCl salt was

obtained following above procedure to obtain TEC. ^{1}H NMR (300 MHz, D_2O) δ 1.05 (d, 24H, -CH(CH_3)$_2$) 2.19 (m, 4H, -CH_2CH(CH_3)$_2$) 2.21 (q, 4H, -NCH$_2$CH_2CH_2N-) 3.25 (d, 8H, -CH_2CH(CH_3)$_2$) 3.59 (t, 8H, NCH_2CH_2CH_2N-) 3.87 (s, 8H, -NCH_2CH_2N-). MS, EI (70 eV), m/z (% relative to base peak) M^+ = 424 (1), 367 (1), 310 (0), 286 (1), 238 (3), 199 (25), 185 (6), 100 (100), 58 (23).

1,4,8,11-TETRAMETHOXYETHYL-1,4,8,11-TETRAAZACYCLOTETRADECANE (TMEC). A solution of cyclam (0.2 g, 0.99 mmol) and K_2CO_3 (1.38 g, 9.9 mmol) in chloroform (10 mL) was treated with a solution of 2-bromomethylethylether (1.1 g, 7.98 mmol) in chloroform (10 mL). The product was obtained as thick oil (0.39 g, yield 90%). White powder form of HCl salt was obtained following above procedure to obtain TEC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (q, 4H, -NCH$_2$CH_2CH_2N-) 2.54 (t, 8H, -N-CH_2CH_2O-) 2.69 (s, 8H, -NCH_2CH_2N-) 2.82 (t, 8H, -NCH_2CH_2CH_2N-) 3.21 (S, 12H, -OCH_3) 3.40 (t, 8H, -CH_2CH_2O-). MS, EI (70 eV), m/z (% relative to base peak) M^+ = 432 (1), 401 (0), 387 (0), 373 (0), 355 (0), 341 (0), 318 (0), 304 (0), 292 (0), 274 (0), 255 (0), 242 (1), 229 (9), 215 (3), 203 (21), 189 (3), 171 (12), 157 (2), 141 (3), 128 (10), 114 (19), 102 (100), 84 (19), 72 (7), 59 (27).

1,4,8,11-TETRAETHOXYETHYL-1,4,8,11-TETRAAZACYCLOTETRADECANE (TEEC). A solution of cyclam (0.2 g, 0.99 mmol) and K_2CO_3 (1.38 g, 9.9 mmol) in chloroform (10 mL) was treated with a solution of 2-bromoethylethylether (1.2 g, 7.98 mmol) in chloroform (10 mL). The product was obtained as thick oil (0.4 g, yield 83%). White powder form of HCl salt was obtained following above procedure to obtain TEC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 12H, -OCH$_2$CH_3) 1.61 (q, 4H, -NCH$_2$CH_2CH_2N-) 2.08 (s, 8H, -NCH_2CH_2N-) 2.55 (t, 8H, -N-CH_2CH_2O-) 2.61 (t, 8H, -NCH_2CH_2CH_2N-) 3.47 (q, 8H, -OCH_2CH_3) 3.48 (t, 8H, -CH_2CH_2O-). MS, EI (70 eV), m/z (% relative to base peak) M^+ = 488 (2), 473 (0), 443 (2), 429 (1), 350 (1), 270 (3), 231 (28), 185 (7), 116 (100), 72 (26).

Radiochemistry

LABELLING. Cyclam (1 mg) was labelled by incubating with stannous chloride dihydrate (5 μg), 1 N Na_2CO_3 (250 μl), and ^{99m}Tc-pertechnetate (~370 MBq/2 ml) for 10 min at room temperature. TMC, TEC, and TPC (1 mg) were labelled by incubating with stannous chloride (10 μg), 1 N Na_2CO_3 (250 μl), and ^{99m}Tc-pertechnetate (~370 MBq/2 ml) for 2 hr at room temperature. Labelling of the other cyclam derivatives was tested under same conditions except the addition of increased amount of stannous chloride up to 100 μg. Labelling efficiencies were checked by paper chromatography as literature method (17) and ITLC-SG (Gelman Co.)/(acetone or saline).

PAPER ELECTROPHORESIS. Each 0.7 μl aliquot of ^{99m}Tc labelled cyclam derivative

was loaded onto Whatman No. 1 paper (2.5 X 20 cm, soaked by 0.1 N sodium phosphate buffer, pH 8) and DC 100 V was applied for 60 min using a horizontal electrophoresis apparatus. Radioactivies on the Whatman No. 1 paper were determined by TLC scanner after drying using heat gun.

STABILITY. The ^{99m}Tc labelled cyclam derivatives were stored at room temperature for 6 hr and the stabilities were checked. To check the stability in human serum, each 0.2 ml aliquot of ^{99m}Tc labelled cyclam derivative (~75 MBq) was incubated with 2 ml human serum for 6 hr in incubator (37°C with 5% CO_2 environment). Radiochemical purity was checked by chromatography with Whatman No. 1 paper/(acetone or saline).

PARTITION COEFFICIENTS. Partition coefficients in octanol were measured separately by adding 100 μl of the ^{99m}Tc labelled cyclam derivatives into a test tube containing 3 ml each of 1-octanol and phosphate buffered saline (pH = 7.4). The test tubes were vortexed 3 min and then centrifuged for 10 min at 1,400×g to separate 1-octanol and water phase. Aliquotes (100 μl) from the 1-octanol and water layers were counted for activity. The partition coefficients (P) were determined by calculating the ratio of cpm/ml of octanol to that of the buffer.

PROTEIN BINDING. *Each 0.1 ml aliquot of ^{99m}Tc labelled cyclam derivative (~37 MBq) was incubated with 1 ml human serum at 37°C for 1 hr. Protein-bound fractions were precipitated by adding 1 ml ethanol and separated by centrifugation (3,000 rpm, 10 min). The radioactivity of each precipitate and supernatant was measured by dose calibrator.*

Animal studies

The animal studies complied with the ethical committee of the Seoul National University Hospital and with national laws relating to the conduct of animal experiments.

BIODISTRIBUTION. Each 0.1 ml aliquot of ^{99m}Tc labelled cyclam derivative (74 kBq) was injected into ICR mice (male, n = 4 per each derivative, body weight = 32.9 ± 1.7 g) through the tail vein. All mice were sacrificed 20 min after injection of the radiotracers. Blood, muscle, fat, heart, lung, liver, spleen, stomach, intestine, kidney, brain, and bone were removed and weighed. Radioactivities of the samples were measured by a gamma counter and tissue concentrations were expressed as percent injected dose per gram (% ID/g) normalized to 20 g body weight. Student's t-test was used for the statistical analysis.

IMAGING. ICR mice (male, ~32 g) were intraperitoneally injected with 5.4 μg ketamine hydrochloride to induce anesthesia. After positioning the mice under the gamma camera (Siemens, U.S.A.) equipped with a 4 mm pin hole collimator, ^{99m}Tc labelled cyclam derivatives were injected through the tail vein. Images were obtained at 0.5, 5, and 10 min.

RESULTS AND DISCUSSION

Synthesis of N,N',N'',N'''-tetraalkylcyclam

All the *N,N',N'',N'''*-tetraalkylcyclams reported herein were obtained with reasonably high yield (83~90%). We used chloroform and K_2CO_3 as a solvent and a base, respectively, according to the reported method (12). In this condition, we did not find any significant production of side products related with carbene which often occurs in chloroform and base reaction. K_2CO_3 should be dried in vacuum oven and ground finely before use for the completion of the reaction. K_2CO_3 was easily removed after reaction because it was insoluble in organic solvent. However, liquid type amine such as triethylamine might be somewhat troublesome to remove because the products are also tertiary amine. And, the hydrogen iodide or hydrogen bromide generated during the reaction could be precipitated as potassium salt rapidly and reduces the chance of side reaction, while the hydrogen iodide or hydrogen bromide sometimes can produce side product in the presence of triethylamine. Other synthesis method of TEC and TPC have been reported (5, 13, 14). However, our method is the only one-step method. The final products were converted to salts of hydrogen chloride to obtain as solid. The solid products were more convenient to use than oil form free base products for the next labelling steps.

Radiochemistry

The cyclam was labelled with ^{99m}Tc with >99% yield in the presence of 5 μg stannous chloride in 10 min as reported in the literature (3). To label TMC and TEC with ^{99m}Tc, additional stannous chloride (10 μg) and incubation time (1 hr) were necessary to obtain a high yield (>97%). TPC was labelled with ^{99m}Tc with 75~86% yield in the presence of 10 μg stannous chloride after 2 hr incubation. The labelling yield of the TPC was not improved with either the change of stannous chloride concentration or incubation time. Higher stannous chloride concentration produced a ^{99m}Tc-colloid. The other cyclam derivatives with larger alkyl and alkylether groups only formed unstable complex with low yield (<30%). The decrease of labelling efficiency and stability with the increase in size of the substituted side-chains is supposed to be related to the increase of the steric hindrance.

We found that all the ^{99m}Tc-labelled cyclam, TMC, TEC, and TPC moved the same distance to cathode by paper electrophoresis, which is evidence that these compounds have an identical positive charge (Fig. 2).

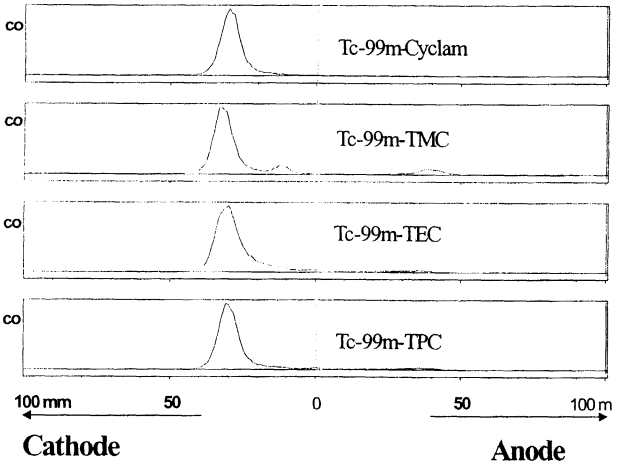

Fig.2. Results of paper electrophoresis. ^{99m}Tc-labeled compounds were loaded at the center position (0 mm).
Following lectrophoresis, the electrophoretograms were obtained by TLC scanner.

The ^{99m}Tc-cyclam has already been reported to have +1 charge with a $Tc(V)O_2$ core (3). With this fact, we concluded that all the ^{99m}Tc-labelled *N,N',N'',N'''*-tetraalkylcyclams in this experiment also have +1 charge with a $Tc(V)O_2$ core similar to the ^{99m}Tc-labelled cyclam.

We compared the lipophilicity of the ^{99m}Tc-labelled cyclam derivatives by octanol distribution. As the size of the side-chain increased, the log P value also increased (Table 1). Protein-binding also increased as the lipophilicity of the labelled compounds increased (Table 1)

Table 1. Results of Octanol Distribution and Protein Binding Experiments of ^{99m}Tc-Labelled Cyclam Derivatives.

Compounds	^{99m}Tc-Cyclam	^{99m}Tc-TMC	^{99m}Tc-TEC
Log P	-1,64	-1.34	-1.24
Protein binding (%)	30.8	35.6	41.6

The numbers denote mean values of duplicated measurements.

Animal Studies

Both the ^{99m}Tc-cyclam and ^{99m}Tc-TEC showed rapid excretion through the kidney (Fig. 3). The rapid excretion of ^{99m}Tc-cyclam and ^{99m}Tc-TMC has been reported by Herzog et al (11). The hydrophilicity of the compounds may contribute to the rapid excretion through the kidney. ^{99m}Tc-TEC showed higher uptake in the liver at 10 min than ^{99m}Tc-cyclam (Fig. 3).

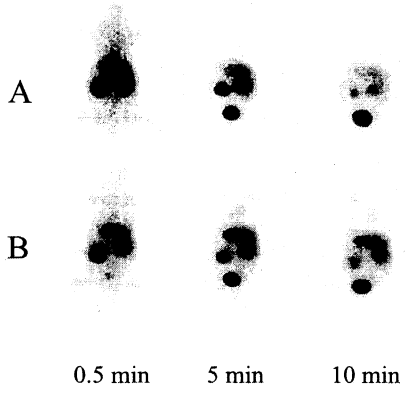

Fig. 3. Gamma-ray images of the mice following injection of (A) ^{99m}Tc-cyclam and (B) ^{99m}Tc-TEC. A pin hole collimator was used for the acquisition.

Biodistribution results also show the higher liver-uptake of ^{99m}Tc-TEC over ^{99m}Tc-cyclam ($p<0.01$, Table 2). The other *N,N',N'',N'''*-tetraalkylcyclam derivatives (^{99m}Tc-TMC and ^{99m}Tc-TPC) also showed higer liver uptake than the ^{99m}Tc-cyclam ($p<0.01$). Basically, the *N,N',N'',N'''*-tetraalkylcyclam derivatives did not show significantly different liver uptake among themselves.

Table 2. Biodistribution of the Cyclam Derivatives in Mice (n = 4)

		^{99m}Tc-Cyclam	^{99m}Tc-TMC	^{99m}Tc-TEC	^{99m}Tc-TPC
Blood	20 min	.2 ± .1	.8 ± .1	.4 ± .0	.4 ± .0
	60 min	.0 ± .0	.5 ± .1	.1 ± .0	.5 ± .0
Muscle	20 min	.1 ± .1	.2 ± .0	.1 ± .0	.1 ± .0
	60 min	.6 ± .9	.1 ± .1	.1 ± .0	.1 ± .0
Fat	20 min	.4 ± .2	.6 ± .1	.7 ± .1	.6 ± .2
	60 min	.8 ± .2	1.2 ± .4	.2 ± .1	1.9 ± .5
Heart	20 min	.1 ± .0	.3 ± .0	.1 ± .0	.2 ± .0
	60 min	.1 .0	.2 ± .0	.0 ± .0	.3 ± .1
Lung	20 min	.1 ± .0	.7 ± .0	.3 ± .1	.6 ± .4
	60 min	.1 ± .1	.4 ± .0	.1 ± .0	.6 ± .1
Liver	20 min	1.2 ± .6	4.2 ± .8	3.2 ± .6	5.0 ± .8
	60 min	.7 ± .2	3.7 ± .8	1.5 ± .2	8.9 ± .5
Spleen	20 min	.1 ± .0	.4 ± .0	.2 ± .0	.4 ± .1
	60 min	.1 ± .0	.4 ± .0	.1 ± .0	.8 ± .1
Stomach	20 min	.2 ± .1	1.0 ± .1	.7 ± .2	.7 ± .2
	60 min	.2 ± .1	3.7 ± 1.0	.3 ± .2	5.0 ± 1.3
Intestine	20 min	1.0 ± .3	2.1 ± .7	2.6 ± .3	3.5 ± .8
	60 min	2.0 ± .3	2.6 ± .7	2.5 ± .3	10.6 ± 1.2
Kidney	20 min	4.3 ± 1.9	7.7 ± .7	7.3 ± .8	11.6 ± 2.3
	60 min	1.9 ± .3	7.5 ± 1.3	3.0 ± .8	13.3 ± 1.3
Bone	20 min	.1 ± .0	.3 ± .0	.2 ± .0	.2 ± .1
	60 min	.2 ± .1	.3 ± .1	.2 ± .2	.3 ± .1

The values denote mean ± S.D.% ID/g.
The labeling efficiency of ^{99m}Tc-TPC was 86%. The other agents showed labeling efficiency of higher than 95%.

In conclusion, we successfully synthesized *N,N',N'',N'''*-tetraalkylcyclam derivatives. However, only the derivatives with alkyl side-chains smaller than butyl could be labelled

with ^{99m}Tc. The ^{99m}Tc-labelled *N,N',N'',N'''*-tetraalkylcylam derivatives excreted rapidly through the kidney in mice. Addition of tetraalkyl group resulted in the increase of liver-uptake.

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REFERENCES

1. Anderegg G. and Blauenstein P. - *Helv. Chem. Acta* **65**: 913 (1982)
2. Thornback J. R. and Theobald A. E. - *Int. J. Appl. Radiat. Isot.* **32**: 833 (1981)
3. Troutner D. E., Simon J., Ketring A. R., Volkert W., and Holms R. A. - *J. Nucl. Med.* **21**: 443 (1980)
4. Moi M. K., Meares C. F., McCall M. J., Cole W. C., and Denardo S. - *J. Anal. Biochem.* **148**: 249 (1985)
5. Bremer K-H., Kuhlmann L., Magerstat M., Schwarz A., and Steinstrasser A. - EP304780A1. (1984)
6. Morphy J. R., Parker D., Alexander R., Bains A., Carne A. F., Eaton M. A. W., Harrison A., Millican A., Phipps A., Rhind S. K., Titmas R., and Weatherby D. - *J. Chem. Soc., Chem. Commun.* 156 (1988)
7. Kastner M. E., Lindsay M. J., and Clarke M. J. - *Inorg. Chem.* **21**: 2037 (1982)
8. Zuckman S. A., Freeman G. M., Troutner D. E., Volkert W. A., Holmes R. A., Van Derveer D. G., and Kent B. E. - *Inorg. Chem.* **20**: 2386 (1981)
9. Deutsch E., Libson K., and Jurisson S. - *Prog. Inorg. Chem.* **30**: 75 (1982)
10. Nunn A. D. "Single photon radiopharmaceuticals for imaging myocardial perfusion" in *Radiopharmaceuticals-chemistry and pharmacology.* Ed. by A.D. Nunn. Marcel Dekker, Inc. New York, 1992, pp97-140.
11. Herzog K. M., Deutsch E., Deutsch K., Silberstein E. B., Sarangarajan R., and Cacini W. - *J. Nucl. Med.* **33**: 2190 (1992)
12. Ketring A. R., Troutner D. E., Hoffman T. J., Stanton D. K., Volkert W. A., and Holmes R. A. - *Int. J. Nucl. Med. Biol.* **11**: 113 (1984)
13. Alcock N. W., Benniston A. C., Grant S. J., Omar H. A. A., and Moore P. J. - *Chem. Soc,, Chem. Commun.* 1573 (1991)
14. Bradshaw J. S., Krakowiak K. E., Izatt R. M., and Zamecka-Krakowiak D. J. - *Tetrahedron Leti.* **31**: 1077 (1990)

